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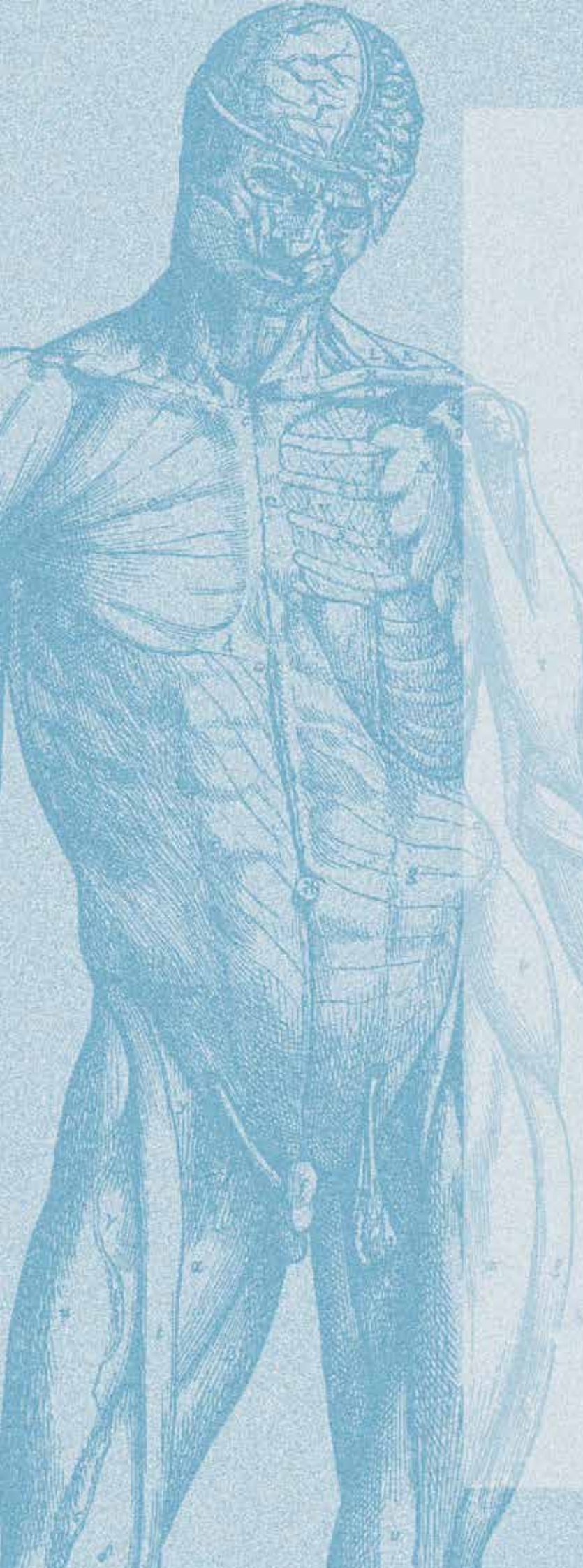

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Editorial

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Treatment expansion for opioid use disorders in the United States

Mark Parrino

American Association for the Treatment of Opioid Dependence - AATOD

As many of our readers know, it has been impossible to pick up a paper or watch television news without hearing a story about the current opioid addiction crisis in America. President Trump recently appointed Governor Christie to be the head of the Commission, focusing on addiction and the opioid crisis. Additionally, HHS Secretary Price nominated Dr. Elinore McCance-Katz to serve as the Assistant Secretary for Mental Health and Substance Use in HHS. Both of these developments are excellent and will be extremely beneficial to our field.

Congress approved the CURES funding package and SAMHSA is currently working with the states and grantees to utilize the first $500 million dollars of funding in 2017.

Some states have extremely innovative models, such as the Vermont Hub and Spoke model, while other states have been challenged in providing access to treatment for their state residents. We have just learned that the state of Mississippi is expanding access to OTPs in order to get the patients the care they need. In the past several years, a large number of Mississippi residents have crossed the border to access care in Alabama and Louisiana. This is welcome news and we are grateful for such a progressive turn in the state's approach to treatment.

We also know that a number of Tennessee residents cross the border to access care in northwestern Georgia. This border crossing caused the Georgia legislature to impose a moratorium on opening new OTPs. This moratorium is expected to be lifted at the end of the current calendar year as the legislature wraps up its findings.

The Commissioner of Health for West Virginia, Dr. Rahul Gupta, recently expressed his interest in developing a comprehensive plan to reduce the number of opioid related deaths in his state. I recently wrote Dr. Gupta, urging him to lift the longstanding moratorium, which has prevented the development of new OTPs in West Virginia since 2008.

While we are in an age of conflicting interests and a growing sense of urgency in order to protect our citizens from the ravages of opioid addiction, we also need to be clear in following evidence based practices and effective policies. Regardless of the state you live in, we need a balance of well-coordinated efforts with prevention, treatment and enforcement. These have always been the three essential policy cornerstones for any effective policy in this field.

We also need to be careful about advancing one addiction treatment medication at the expense of another. There are only three federally approved medications to treat opioid addiction. They all have value and they all should be used at different times in the experience of patient care depending on what the individual needs. Illustratively, Vivitrol (Naltrexone) represents an excellent medication for a former opioid addicted inmate, who has been in jail for some time and is about to be released. Many inmates generally have a fear of relapse upon release from long

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term incarceration even though they have not used opioids for some time. There are a number of correctional facilities that are using Vivitrol injections before the inmate is released. Once again, the key here is to ensure that the patient gets access to a referral so that they can continue their treatment with Vivitrol or other medications, which are deemed medically appropriate and effective. A number of correctional facilities are also working with treatment providers so that inmates with opioid use disorders get access to methadone and buprenorphine.

While methadone maintenance is still considered the "gold standard" of medications to treat this disorder, there are a number of people who have forgotten that it exists and do not factor it into their plan to treat this disorder. The state of Wyoming comes to mind as the recent recipient of a SAMHSA grant. A recent newspaper story indicated that such treatment providers do not believe that methadone is a safe medication to treat this disorder.

Buprenorphine is an excellent medication and access to such medication has increased through DATA 2000 practices. Once again, all of these medications should be used with effective and well-coordinated services.

Ultimately, there will be many discussions about what works best for patients and how the system should function in an integrated system. The only way we are going to get a handle in dealing with an epidemic that has taken 25 years to develop, is to be clear in setting realistic goals about what can be done.

Finally, financial and workforce resources also need to be available as treatment access increases.

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Case Report

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Capgras syndrome in a heroin addict. A case study

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Summary

Background: Capgras syndrome is an extremely rare clinical manifestation. A Capgras delusion can be associated with psychiatric or neurological disorders, with drug therapy or toxicities, metabolic conditions, or nutritional deficiencies, and it is difficult to diagnose. In addition, substance use can mimic or mask symptoms of other psychiatric disorders and can lead to the misdiagnosis or underdiagnosis of other psychiatric conditions. **Case Report:** A drug user with a history of several compulsory hospital admissions to psychiatric hospitals due to violence and physical attacks on others, failed to comply with prescribed treatment in the community, was restarted in directly observed daily therapy combined with stabilization methadone treatment and antipsychotic treatment. **Conclusions:** Although heroin addiction is a treatable condition, both heroin addiction and methadone treatment are still strongly stigmatized by the lay public, general opinion, patients, patients' family members, and those with professional qualifications such as health professionals. This is the first published case of Capgras syndrome in a heroin addict where daily directly supervised methadone treatment helped the drug user to adhere to outpatient antipsychotic treatment integrated with methadone in such a way as to improve compliance and make it possible to manage conditions involving severe risks.

Key Words: Capgras syndrome; heroin addiction; opioid agonist treatment

1. Introduction

In 1923 Jean Marie Joseph Capgras, together with Jean Reboul-Lechaux, reported the first description of Capgras syndrome (CS) as a case of l'illusion des sosies ('the illusion of doubles') in a female patient aged 53 who held firm to a delusional belief that her husband and daughter, but later also police, her neighbours and even herself, were being impersonated and replaced by a host of doubles [9]. CS is classified as being one of the delusional misidentification syndromes. Capgras delusion is clinically distinguished by the misidentification of one or more individuals, and by the delusional belief, which may be transient, recurrent or permanent [20, 25], that the misidentified person/s have been replaced by impostors, who are generally perceived as persecutors [25, 27].

Those so affected misidentify people close to them – people who are usually part of their immediate environment, such as family members, other people who play an important role in their life (in some cases even including themselves), animals, places, objects (all those counterparts with whom the patient has a strong affective bond) – as a result of the patient's delusional belief that they have been replaced by substitutes (better described as doubles or impostors) or else have been transformed [25, 37, 46]. In the course of time, the number of misidentified persons tends to increase and sometimes reaches the extreme of including all the patient's acquaintances [25].

Each substitute is experienced as being similar to the original in appearance and behaviour; patients describe imperceptible differences between the original person and the impostor, who appears to be physically identical with the family member or other people who have been replaced, but not that actual person [37, 46]. The originals may be idealized, while anger and aggressive behaviour may be expressed towards the substitutes. Patients usually maintain clear consciousness, and apparently their cognitive functions

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are intact, but they become paranoid, hostile and full of mistrust, sometimes with feelings of depersonalization, derealization and emptiness, so making the task of diagnostic assessment particularly difficult [46].

Capgras and Reboul-Lechaux considered the phenomenon as centring on affective response, and as involving an interpretative illusion, rather than as being due to a defective perceptual process [9, 46]. Various theories attempted to explain the etiology of the Capgras delusion, ranging from neurological approaches to psychodynamic ones [22, 25]; further observations on cases of CS related to organic disorders made the psychodynamic hypothesis difficult to sustain [25].

2. Case Report

The case is that of a patient with no positivity in his family for drug abuse or psychiatric disorders, while his personal medical history was positive for drug use, psychiatric disorder and other diseases. His medical history is described here on the basis of medical and imprisonment records, his comments and reports supplied by his family.

A 34-year-old divorced, unemployed male patient, with court procedures still open for offences and criminal acts, who had performed public works in serving alternative sentences, is now living with his parents and younger daughter, after being deprived of the custody of his daughter, which was later granted to his parents.

The patient has had a long history of drug use. Since adolescence he has been abusing caffeine, nicotine, alcohol, cannabis, MDMA, heroin, and later cocaine, benzodiazepines and zolpidem. When he was 19 years old, heroin addiction was diagnosed and he was then treated with opioid agonists. At that time no other psychiatric history had been recorded. During the last 15 years the patient has been in various different treatments for heroin addiction; the 'revolving door syndrome' developed due to his wandering from one treatment to another, starting from outpatient opioid agonist treatment, and going on to inpatient detoxification and consequent residental drug-free treatment in a community recommended by a psychiatrist, in which he took part abroad, and treatment in prison.

In June 2009, during inpatient detoxification treatment, psychotic disorder was recorded for the first time; the patient abandoned detoxification and refused antipsychotic treatment, while he continued for a very short time to perform clinical checks on abstinence through rapid testing on the metabolites of drugs in urine. In November 2009 he was treated in hospital for the infection of a drug injection site on the sole of one foot.

Hospitalization in a psychiatric hospital was first documented in 2011, on that occasion being due to the verbal threats he had made against his father. After sedation and antipsychotic treatment because of a possible psychotic episode due to cocaine use, he was released after 6 days, but placed under special control. Quantitative positivity for methadone, heroin and cocaine in blood samples was found.

During the period 2011-2014 this patient underwent as many as 7 enforced admissions to psychiatric hospitals as a result of violence and physical attacks on others; on all these occasions sedation and special measures were prescribed. Minor abnormalities were documented in EEGs and head CTs, but no further information were reported. In 2013 there was compulsory psychiatric treatment of the patient, who had to be detained in hospital for treatment without any possibility of obtaining an informed consent document, first when he was abroad, during his residential long-term treatment in a drug- and medicine-free therapeutic community, then after a transfer of residence back to his own country. Compulsory measures had to be performed to make possible the administration of medical treatment to the patient in order to prevent him becoming a danger to himself or others. During the treatment in his own country, patient was later transferred from one psychiatric hospital to another because of physical attacks on patients and staff.

After every discharge from hospital this CS patient stopped his antipsychotic treatment and failed to comply with prescribed treatment in the community, so becoming classified as non-compliant because of his lack of insight; in general he tended, in the 2011-2014 period, to be frequently in and out of a series of psychiatric hospitals.

In 2014, at the moment of a compulsory admission to a psychiatric hospital, the suspicion that the patient might have Capgras syndrome was recorded for the first time. In 2014 this patient came to our attention, and polydrug use, addiction, chronic hepatitis C, personality disorder, chronic psychosis and Bell's palsy were documented. At that time he was performing public works in serving sentences alternative to prison; while awaiting trial, he reported abstinence and declined antipsychotic and opioid agonist treatment, but he did ask for benzodiazepines and zolpidem. In 2014, 30 mg of methadone were introduced as

initial dose (the patient refused to increase this daily dosage, and, after methadone therapy had been introduced, the patient's urine samples proved to be negative when testing for heroin metabolites), and a health care worker observed the patient swallow every dose of the prescribed methadone. From 2014 methadone maintenance was combined with the introduction and regular application of a depot preparation of a neuroleptic drug, initially a 40 mg intramuscular injection of flupenthixol decanoate and later, due to the inaccessibility of that drug on the market, a 200 mg intramuscular injection of zuclopenthixol decanoate every 4 weeks; after that, no further enforced psychiatric hospitalization was requested. Our patient, at every application of intramuscular therapy, tried to stop the treatment, and peroral antipsychotic therapy was never possible due to his non-compliance, whereas he did accept methadone, biperiden and quetiapine.

The mental status examination during outpatient psychiatric visits was unremarkable, and our patient seemed rational in other respects, as he demonstrated no cognitive impairment. His cognitive functions were adequate, but he did not show insight. He showed awareness of his setting and at all times cooperated satisfactorily in communication, while remaining correctly oriented in following the conversation. His spontaneous speech had decreased, though he responded to questions, while, when asked about his psychopathological symptoms, he always denied having produced them. His mood was irritable and his affect was normal. His associations were generally regular; his thought content showed preoccupation with the condition of his mother, but he rarely spoke about that. He revealed that in the past he had frequently reported to others "My mother is not my mother, she seems like her but is not her." and that during his stay in prison he asked the health authority for help in unmasking the impostor. After 2 years of regular depot therapy he was still convinced that "his mother is not his mother" and "asked for help in performing DNK analysis to demonstrate the duplicate". After the patient received antipsychotic treatment, his relatives reported periods when he was prepared to collaborate and help instead of being hostile, while still showing permanent mistrust but, in those periods, without aggressiveness or violence.

3. Discussion

CS is an extremely rare clinical manifestation and it is difficult to diagnose, because it is associated with primary psychiatric disorders such as paranoid schizophrenia [4, 11, 41, 54], schizoaffective disorder [4, 23, 41] and affective disorder [12, 27, 31, 52]. In recent years, besides psychiatric disorders CS has been associated with organic illnesses, neurological disorders e.g., cerebrovascular accidents [13, 24, 29], cerebrovascular disease [17], tumours (e.g. pituitary tumour [51]), epilepsy [19, 21, 28], multiple sclerosis [47], head injuries [5], intracerebral haemorrhage [27], arteriovenous malformations, delirium, migraine [1, 7, 20, 46, 56] and various other pathologies [12], including metabolic diseases [13], infectious diseases [15], septic shock [15, 27], and Basedow disease [10]. Case studies on CS reported it as being associated with a range of neurodegenerative diseases: Alzheimer's disease [2, 25, 27, 30, 32, 38, 53], Lewy body dementia [27, 34, 53], Parkinson's disease.[27, 39], dementia not otherwise specified [27], frontotemporal dementia [27], aphasic dementia [27]. Other case studies on CS reported it as being associated with toxicity, for instance in cases of intoxication with drugs like lithium [8, 35, 43] or a combination of lithium and IMAO [43, 8], during disulfiram treatment [16], diazepam treatment [50], morphine treatment [3], use of substances [6, 27, 37, 40, 49], alcohol consumption [33, 44], methamphetamines [6], synthetic cannabinoids [55], cocaine [37, 42], and ketamine [14]. Capgras delusion usually occurs as part of a psychiatric disorder [10-12, 25]; as many as one-third of all reported cases of CS occur because of intoxications, brain injuries, dementia or organic conditions [25, 27]. CS has been recognized as a clinical entity, rather than a symptom of other illnesses [25]. Those so affected usually remain mentally lucid in other aspects of their social life, with small or delusional differences having an excessive effect on their perception of the physical appearance, behaviour and clothing of the relative and/or the alleged impostor, so leading to the delusional conviction [25].

The case described above is CS with various possible combinations of substrates: psychiatric pathology (functional conditions), toxicology (substance use) and/or neurological organic conditions.

From a neurochemical standpoint it has been proposed that increased activity in the dopamine circuit (e.g. due to stimulants like cocaine, with ensuing hyperactivation of the dopaminergic circuit) is likely to be associated with CS [16, 45]. Neuropsychological impairment (brain disfunction) has been observed in psychiatric disorders, neurodegenerative disease and in CS [7, 37]. When a neuroanatomical approach has been taken, CS has been associated with lesions in both hemispheres [48], and in the frontal, temporal

and parietal lobes [26]. One hyothesis that has been proposed is that a brain lesion interferes with the patient's ability to sense a familiarity previously felt towards the significant other, while the ability to identify that person remains intact [22], CS may be related to impaired recognition of a familiar face, subserved by the posterior cingulate/precuneus cortex, and impaired reflection about personally relevant knowledge related to a face [25].

However constant the delusion may prove to be – and there are cases of delusion that continue to persist for years after a period of abstinence and antipsychotic treatment – its most likely cause lies in the psychiatric pathology substrate rather than in toxicology (substance use) or in being drug-related.

4. Conclusions

CS is a rare clinical condition among the general population, and it is difficult to diagnose [25]. To the best of our knowledge, this is the first reported case of CS in a heroin addict. CS can be associated with, or be secondary to, the psychiatric or neurological disorders, drug toxicities, metabolic conditions, nutritional deficiencies, and it often goes undiagnosed. Those affected by CS should receive a complete assessment regarding an evaluation of the underlying etiology. The treatment is directed towards the etiology and relief of psychotic symptoms. Capgras delusion must be distinguished from prosopagnosia, an impairment of familiar face recognition [25].

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Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The study does not have IRB review/approval; this study does not require ethics committee approval because 'Case reports' do not require ethics committee approval but an informed consent document signed by patients.

Note

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Opioid maintenance therapy with methadone and levomethadone - sexual dysfunction and treatment satisfaction

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Summary

Background: Sexual dysfunction (SD) is a common adverse effect of opioid maintenance therapy (OMT). Little is known about its impact on treatment satisfaction. **Aim:** To explore SD and its impact on treatment satisfaction and wish for advice on that subject in patients receiving OMT compared with a group of patients with other substance use disorders (control group). **Methods:** 95 patients with opioid dependence receiving OMT and 90 patients with other substance use disorders were included. A self-rating instrument as well as the International Index of Erectile Function (IIEF) and the Female Sexual Function Index (FSFI) were applied. **Results:** In the OMT group, 69.1% of the patients reported to suffer from SD, in contrast to 18.2% in the control group ($p<0.001$). With 40.7%, OMT was the most quoted reason for SD. 55.6% of the patients in the OMT group reported to be willing to quit OMT because of SD. Significantly more patients in the OMT group claimed a wish for advice on SD ($p=0.004$). In the OMT group, 15.6% of the patients reported to have been interviewed by a doctor concerning this subject, in the control group 4.9% did so ($p=0.052$). Regarding the IIEF, the patients in the OMT group were significantly less satisfied with their sexual life than patients in the control group ($p=0.023$). The FSFI revealed no differences. **Conclusion:** SD is common in OMT in comparison with other substance use disorders and may have a pejorative influence on treatment satisfaction. Despite the patients' wish, advice on the subject was often not provided.

Key Words: Sexual dysfunction; OMT; treamtent satisfaction

1. Introduction

Opioid maintenance treatment (OMT) is the most frequently used treatment of chronic opioid dependence [1]. In Germany, Methadone and Levomethadone are the mainly used drugs in this indication. OMT has proven its efficacy, e.g. concerning reduction of heroin consumption, decrease of mortality and criminal activity [9, 20, 29].

Besides the positive effects, various adverse effects occur under OMT. Frequent are psychological symptoms such as tiredness, irritability and lack of motivation as well as vegetative side effects such as hyperhydrosis and cardiac side effects [4, 11, 26].

A further relevant side effect under OMT with regard to quality of life is sexual dysfunction. A review of the literature reported prevalences of sexual dysfunction from 14-81% in patients with chronic opioid dependence treated with OMT [13]. In a meta-analysis of 16 studies with 1570 patients under OMT a prevalence of 52% of SD was found [32]. Zhang et al. found an increase of erectile dysfunction and libido disorder after initiation of OMT [33]. After 6 month of OMT, Parvaresh et al. reported a significant increase of sexual dysfunction in patients receiving OMT [21]. Other studies found a significantly higher rate of sexual dysfunction, reduced basal plasma levels of testosterone and increased prolactin levels among heroin-dependent patients on OMT, as compared with healthy controls [12, 15, 28].

Sexual dysfunction is not only a problem related to OMT, but also occurring in opioid dependence without treatment and other substance use disorders. A review of the literature concerning sexual dysfunc-

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tion in patients with alcohol dependence found prevalences from 40-95.2% and from 34-85% in patients with opioid dependence [13]. Among others a significantly higher prevalence of erectile dysfunction in patients using amphetamine compared to healthy controls was found [8].

For several psychotropic drugs (for example antipsychotics and antidepressants) sexual dysfunction is a known side effect with a relevant impact on treatment satisfaction and adherence [2, 24]. Despite the high prevalence of sexual dysfunction under OMT little is known about its effects on treatment satisfaction. In a qualitative exploration in 27 patients Xia et al. focused on sexual dysfunction after the beginning of OMT (one third of the patients reported a slight amelioration of their sexual function) and 6 to 12 month after onset of treatment, where mostly a pejorative effect, mainly as loss of libido and orgasmic function, was reported. The authors described that none of the participating clinics provided advice on sexual dysfunction, but reported a patients' wish for support hereof [30]. From different clinical domains it is known that in spite of wish for advice, in the clinical practice, sexual dysfunction is often not spoken about [6, 16].

In our survey investigating patients with opioid dependence receiving OMT, as one endpoint we focused on sexual dysfunction and its impact on treatment satisfaction and investigated a possible wish for advice on the subject. Further on, we compared the results to a group of patients with other substance use disorders, in order to find out whether sexual dysfunction and its impact on treatment satisfaction play a specific role in OMT patients. To our knowledge, no other study explored this subject so far in this group of patients and compared it to a control group.

2. Methods

The survey was performed from November 2013 to September 2014. Included were subjects (male and female), aged 18 to 75 years with a diagnosis of opioid dependence according to ICD-10 criteria in current OMT with methadone or levomethadone or with at least one other substance use disorder apart from opioid dependence and without current opioid consumption. Further inclusion criteria were the ability to comply in the study and sufficient knowledge of the German language.

All of the patients were contacted during detoxification in in-patient treatment. None of the patients detoxified from the OMT. Patients were informed about the questionnaire in oral and written form. The questionnaire was completed anonymously without the help of staff and collected in a sealed box. The study was approved by the local ethics committee.

2.1. Instruments

An anonymous questionnaire was employed to collect data. The questionnaire was designed for the study by the authors and was used in this study exclusively. A grouping question (time span) was used to collect age in order to maintain professional secrecy. Moreover, multiple choice questions and open questions were utilized. The questionnaire was divided in a general and a specific part. In the general part, demographic data and clinical parameters on the history of the substance use disorder and OMT was collected. The specific part contained questions on self-reported sexual dysfunction. Concerning self-reported SD, patients were asked if they perceived sexual dysfunction and what they consider as the reason for SD. In addition, the patients in the OMT group were asked about the possible influence of OMT and if they would like to quit OMT because of SD. Further on, the specific part contained questions on a possible wish for advice concerning sexual dysfunction and if this subject was addressed by a clinician. Apart from the variables sex and belonging to the OMT or control group, which were considered while handing out the questionnaires, all other items were filled in by the patients themselves.

Male patients additionally filled in the International Index of Erectile Function (IIEF). The IIEF refers to the last 4 weeks. It contains 15 items which cover 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The IIEF is a validated and widely used questionnaire to record erectile dysfunction [23]. For the female patients, the Female Sexual Function Index (FSFI) [22] was used. The questionnaire assesses data on 6 domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain [22]. For several items of both questionnaires, sexual intercourse within the last 4 weeks before the interview is necessary to evaluate the questionnaire. Due to this, patients who did not have sexual intercourse within the last 4 weeks were excluded from the analysis of intercourse-dependent domains. The number of missing values is partly explained by that.

Additional information was collected regarding risk behaviour concerning sexual activities and with injection needles, these data was reported elsewhere

[25].

2.2. Data analysis

Data was analyzed using the IBM® SPSS® Statistics Version 22.

The study approach was explorative. Differences between groups were investigated using the Fisher's Exact test. For normally distributed continuous variables mean and standard deviation were reported, means were compared using the t-test. For non-normally distributed continuous variables median and interquartile ranges were reported. To detect differences between groups we used Mann-Whitney U-Test. A p-value <0.05 was considered significant.

2.3. Matching

As a higher age is discussed as important predictor for sexual dysfunction [27], it was defined as a group-matching factor. The investigated groups were not supposed to differ significantly in age (p>0.1). Initially the group of patients with other substance use disorders was significantly older than the OMT group which was due to the male participants (p=0.024). Consequently, 9 out of the 71 male patients of the control group were excluded incidentally.

After application of inclusion criteria and group-matching, the sample was composed of 185 patients of the 220 initially participating subjects.

3. Results

3.1. Demographic characteristics

In total, 185 patients were included in the analysis. 95 were in the opioid maintenance treatment group (OMT group), 90 in the control group.

In the OMT group 66 (69.5%) of the patients were male, 29 (30.5%) female. All of the patients were receiving methadone (N=41, 43.2%) or levomethadone (N=54, 56.8%). The average dosage of OMT was 111.3 mg ± 45.1 mg (in equivalent methadone dosages). The average duration of OMT treatment was 5.4 (IQR 7.6) years. The mean duration of opioid dependence was 14.5 (IQR 12.5) years.

In the group of patients with other substance use disorders (control group) 62 (68.9%) of the patients were male, 28 (31.1%) female. In table 1, an overview of the present substance use disorders is provided.

Table 1: Descreption of the group of patients with other substance use disorders

Substance use disorder*	N (%)
Alcohol	79 (87.8)
Cannabis	18 (20.0)
Cocaine	11 (12.2)
Benzodiazepines	8 (8.9)
Stimulants	6 (6.7)
Others	2 (2.2)
Multiple	28 (31.1)
*multiple answers possible	

3.2. Comparison of the OMT group and group of patients with other substance use disorders

Groups did not differ with regard to age, sex, graduation, professional life, parenthood, partnership and sexual intercourse in the last 4 weeks. In the control group there were more patients with completed job training (p<0.001) (Table 2).

Concerning health condition and characteristics of the substance use disorders Hepatitis C occurred significantly more often in the OMT group (p<0.001) whereas diabetes mellitus was more frequent in the control group (p=0.006). Concerning concomitant substance use, in the OMT group use of cannabis (p=0.031), benzodiazepines (p<0.001), heroin (p not calculable), cocaine (p=0.033), nicotine (p=0.004) and multiple substance use (p<0.001) was more frequent, whereas consumption of alcohol occurred more often in the other group (p <0.001) (Table 3).

3.3. Self-reporting of sexual dysfunction and satisfaction with sexual life

158 patients provided information on subjectively perceived sexual dysfunction. In the OMT group, 69.1% (N=56) of the patients reported to suffer from sexual dysfunction, whereas only 18.2% (N=14) in the control group did so (p<0.001). 62.4% (N=53) of the patients in the OMT group reported that OMT had a negative effect on their sexual life. With regard to reasons for subjectively perceived sexual dysfunction, OMT was the most often quoted reason (40.7%, N=33). 33.3% (N=27) thought that concomitant substance use was the reason for sexual dysfunction. 55.6% (N=40) of the patients in the OMT group reported that they would like to quit OMT because of sexual dysfunction.

Using the International Index of Erectile Func-

Table 2: Comparison of the groups

	Total N=185	OMT group N=95	Other substance use disorders N=90	p[1]
Age (years)				
18-20	3 (1.6)	1 (1.1)	2 (2.3)	
21-30	46 (25.3)	25 (26.6)	21 (23.9)	
31-40	45 (24.7)	28 (29.8)	17 (19.3)	
41-50	64 (35.2)	34 (36.2)	30 (34.1)	0.138[2]
51-60	21 (11.5)	5 (5.3)	16 (18.2)	
61-70	2 (1.1)	1 (1.1)	1 (1.1)	
71-75	1 (0.5)	0 (0)	1 (1.1)	
Gender				
Male	128 (69.2)	66 (69.5)	62 (68.9)	>0.999
Female	57 (30.8)	29 (30.5)	28 (31.1)	
School-leaving qualification	147 (87)	74 (86)	73 (88)	0.820
Completed Training	99 (58.2)	36 (42.9)	63 (73.3)	<0.001
Current Occupation	27 (15.7)	10 (11.6)	17 (19.8)	0.208
Current Partnership	61 (34.5)	37 (40.7)	24 (27.9)	0.083
Own Children	73 (40.1)	36 (38.3)	37 (42)	0.651
Sexual intercourse within the last 4 weeks	86 (48.9)	48 (54.5)	38 (43.2)	0.175

Data presented as n (%).
Missings: age N=3, school-leaving qualification N=16, completed training N=15, current occupation N=13, current partnership N=8, intercourse N=9, own children N=3
[1] p<0.05 is considered significant, significant p-values are shown in bold
[2] Comparison of OMT group and control group with age groups 18-40 vs. 41-75 years

tion (IIEF) the patients in the control group were significantly more satisfied with their sexual life than patients in the OMT group (p=0.023). There was a trend to higher sexual desire in the control group (p=0.093). Concerning erectile function, orgasmic function, intercourse satisfaction and overall satisfaction there were no significant differences between the groups (Table 4).

Using the Female Sexual Function Index (FSFI) no difference was found between the OMT group and the group of patients with other substance use disorders. Due to the requirements of the questionnaire (i. e. sexual intercourse in the last 4 weeks) the following missings occurred: lust N=3, arousal N=21, lubrication N=27, orgasm N=29, sexual intercourse N=2, satisfaction N=8, pain N=2, overall score N=12.

3.4. Wish for advice on sexual dysfunction

51.4% (N=37) of the patients in the OMT group claimed a wish for advice on sexual dysfunction, significantly more than in the control group (25.5%, N=14, p=0.004). In the OMT group, 15.6% (N=14) of the patients reported to have been interviewed by a doctor concerning this subject, in the control group 4.9% (N=4) of the patients did so (p=0.052).

4. Discussion

The aim of our explorative study was to assess sexual dysfunction in patients with chronic opioid dependence currently receiving OMT in order to evaluate its impact on treatment satisfaction as well as the wish for advice compared to patients with other substance use disorders.

Approximately two third of the patients in the OMT group reported to suffer from sexual dysfunction, whereas significantly less of the patients in the control group did so. The difference in the prevalence of self-reported sexual dysfunction hints towards a direct effect of the substance used for OMT (in our study methadone or levomethadone). This link is also seen by the patients themselves who mainly attributed SD to OMT. This is in line with the study of Zhang et al., which reported a worsening of sexual function after onset of OMT [33].

In our study, both of the groups were of good comparability. Critically, groups did not differ in

Table 3: Health condition and characteristics of the substance use disorders

	Total N=185	OMT group N=95	Other substance use disorders N=90	p[1]
Body Mass Index (Median, IQR)	23.8 (5.7)	23.8 (5.0)	23.8 (6.4)	0.581
Infectious diseases				
Hepatitis C	39 (22,4)	39 (43,3)	0	<0.001
Hepatitis B	10 (5.7)	9 (10)	1 (1.2)	0.019
HIV	6 (3.4)	5 (5.6)	1 (34.1)	0.212
Diabetes mellitus	7 (4.1)	0	7 (8.2)	0.006
Hypertension	22 (12..8)	9 (10.3)	13 (15.3)	0.368
Intake of regularly prescribed medication	82(45.3)	40 (43.5)	42 (47.2)	0.656
Concomitant substance use (last 4 weeks)				
Alcohol	128 (69.9)	54 (56.8)	74 (84.1)	<0.001
Cannabis	65 (35,5)	41 (43.2)	24 (27.3)	0.031
Benzodiazepines	60 (32.8)	50 (52.6)	10 (11.4)	<0.001
Heroin	39 (21.3)	39 (41.4)	0	
Cocaine	33 (18)	23 (24.2)	10 (11.4)	0.033
Amphetamine	17(9.3)	12 (12.6)	5 (5.7)	0.130
Nicotine (smoking cigarettes)	159 (90.3)	87 (96.7)	72 (83.7)	0.004
Multiple substances	96 (52.5)	65 (68.4)	31 (35.2)	<0.001

Data presented as n (%).
Missings: BMI N=6, infectious diseases N=11, intake of regularly prescribed medication N=4, concomitant substance use N=18, cigarette smoking N=9
[1] p<0.05 is considered significant, significant p-values are shown in bold

variables well known to impact on sexual function, namely age, sex, social situation and overall medical condition. An interesting finding is that current concomitant substance use was higher in the OMT group except for alcohol (as most of the patients in the control group suffer from alcohol dependence). One possible explanation might be that by using drugs, patients try to enhance their sexual performance or to level pre-existing sexual dysfunction [17-19]. It has been reported that illicit drug users presented a high prevalence of SD prior to initiation of drug use. La Pera et al. concluded that depending on the severity of SD, a higher proportion of patients claimed that sexual dysfunction had influenced their decision to

Table 4: International Index of Erectile Function, IIEF

	Total N=128	OMT group N=66	Other substance use disorders N=62	p[1]
Orgasmic function (Median, IQR)	10.0 (2.0)	10.0 (3.0)	10.0 (2.0)	0.452
Sexual desire (Median, IQR)	7.0 (3.0)	6.0 (3.0)	7.0 (3.0)	0.093
Overall satisfaction (Median, IQR)	8.0 (4.0)	7.0 (5.0)	9.0 (3.0)	0.023
Participant with sexual intercourse within the last 4 weeks	N=58	N=33	N=25	
Erectile function (IQR)	28.0 (5.0)	27.5 (5.0)	29.0 (5.0)	0.344
Satisfaction with sexual intercourse (mean, SD)	11.1 (2.7)	10.9 (3.2)	11.4 (2.1)	0.238
IIEF overall score (Median, IQR)	64.0 (10.0)	63.5 (13.0)	66.0 (8.0)	0.322

Data presented as n(%).
Missings: orgasmic function N=50, sexual desire N=7, overall satisfaction N=72, sexual intercourse N=7, erectile function N=11, overall score N=29
[1] p<0.05 is considered significant, significant p-values are shown in bold

initiate drug use [18].

More than half of the patients in the OMT group indicated that they would quit OMT because of sexual dysfunction. This is in line with other studies, which defined SD as important factor for treatment discontinuation [21, 31]. Likewise, the pejorative impact of sexual dysfunction on the subjectively perceived quality of life in OMT patients has recently been described by Teoh and collegues [27]. Patients that consider their quality of life diminished are more likely to abandon the treatment. However, treatment discontinuation or even cessation of OMT is known to increase the risk of relapse and mortality in opioid dependent patients [10, 20] . In their study, Gutwinski et al. found that patients generally considered OMT beneficial with regard to physical and mental health. Nevertheless, the patients' wish to end OMT on the long term was significantly stronger than estimated by staff members [14]. In the clinical practice, it is important to address the patients' perspective concerning the OMT including sexual dysfunction routinely. Unfortunately, questions concerning sexuality are often avoided by clinicians [7, 27]. In our survey, more than half of the patients in the OMT group claimed a wish for advice on sexual dysfunction, which was significantly more than in the group of patients with other substance use disorders. Only 15.6% of the patients in the OMT group reported to have talked to a doctor concerning the subject. This is in line with the findings of Xia et al., who observed a lack of providing advice on sexual dysfunction in four specialized OMT-clinics [30]. Also in the control group there was a clear discrepancy between patients expressing a wish for advice on sexual dysfunction and patients indicating to have had an interview by a doctor concerning that subject. This result corresponds to findings from other medical domains which indicate that sexual dysfunction is often neglected in the clinical routine [6, 16].

In patients with OMT who suffer from sexual dysfunction, several strategies could be applied. There is a hint towards dosage and occurrence of sexual dysfunction: higher dosages seem to favor emergence of sexual dysfunction [3, 33]. In OMT patients concerned with sexual dysfunction, a reduction of dosage could be helpful. In addition, there are studies reporting lower rates of sexual dysfunction when buprenorphine is used for OMT: Yee et al. found that buprenorphine caused less sexual dysfunction than methadone [31]. Another study reported no decrease in plasma testosterone levels in buprenorphine-treated patients, which is recognized to cause sexual dysfunction in methadone treatment [5]. In patients who suffer from sexual dysfunction, a switch to buprenorphine could be considered.

Our study has some limitations. First, self-rating questionnaires constitute a manner of inquiry that allows a high level of privacy and encourages sincerity (in comparison to interviews, for example). Thus, as the questionnaires are self-rating instruments, no information from the sexual partner was obtained. Second, the study sample consisted of patients undergoing in-patient detoxification treatment. Therefore, the sample is not comparable to the overall OMT patient population. On the other hand, this design allows the recruitment of a well comparable control group concerning psychosocial factors. To our knowledge, no other study explored such a comparison group so far. In the third place, it would have been of interest to measure serum testosterone levels in order to objectify sexual dysfunction. At last, a bigger sample size, above all for the evaluation of IIEF and FSFI (due to the requirements of the questionnaires, i. e. sexual intercourse in the last 4 weeks), would have made results more reliable. Due to the explorative design of the study, adjustment for multiple testing was spared. As a consequence, the results have to be interpreted cautiously and require replication.

5. Conclusions

In summary, sexual dysfunction is not only prevalent in opioid dependence but also in other substance use disorders. Nevertheless, our findings suggest a peculiar relevance of sexual dysfunction in patients receiving OMT. Sexual dysfunction may have a pejorative influence on treatment satisfaction, and, subsequently, may lead to treatment discontinuation or cessation. Sexual dysfunction might be a factor influencing the choice of substance and its dosage as well as the patients' wish to quit the OMT. Further on, the majority of patients expressed a wish for advice on the subject which was often not provided. Thus, advice on sexual dysfunction should be offered routinely by professionals working with OMT patients, namely before initiation and during the treatment.

Future studies may address the question if increased monitoring of sexual dysfunction and advice on the topic in the clinical practice can improve patients' treatment satisfaction and treatment adherence.

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Conflict of interest

All authors have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The study has IRB review/approval.

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On the long-term status of treatment-seeking, heroin addicted patients: A 22-year follow-up study on mortality and drug use in Portugal

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Summary

Background: Evidence showed that problematic drug users, in particular heroin users, have a higher risk of re-engagement in drug use and consequent death than the general population. **Aim:** Our aim was to perform a descriptive follow-up analysis to assess mortality and current drug use by reviewing over two decades of treatment admissions. **Methods:** We considered the cohort sample of heroin treatment-seeking patients from 1992 to 2013 that completed the clinical protocol (N= 627 patients). A total of 222 cases (35.4%) of heroin users were traced. A telephone post-treatment 22-year follow-up interview was then performed for each of these cases to allow assessment of current drug use in relation to mortality. **Results:** The follow-up analysis estimated a percentage frequency of mortality of 13.1%, with attribution of the main cause of death revealing a connection with HIV/AIDS. Comparative analyses suggested the potential impact of some clinical conditions on drug-related mortality, namely, HIV infection, intravenous drug use, sharing of needles, unemployment and a greater number of years of heroin and other drug consumption when compared with the population of survivors. Among those who were alive, 17.4% reported that they had been using heroin and 15.5% cocaine in the previous 30 days. Our baseline and follow-up data confirm that around 10% of the heroin-addicted population presented a drinking problem. **Conclusions:** Our long-term study clearly shows the burden that HIV infection and intravenous drug use have imposed on the country in terms of mortality and morbidity. Moreover, the rate of alcohol and drug use over the follow-up period suggests that many aging heroin users are in need of continuous clinical attention.

Key Words: Heroin addiction; drug use patterns; mortality; follow-up

1. Introduction

For many years now drug addiction issues have been an unsettling focus of political agendas. The drug abuse problem turned out to be one of the main concerns of Portuguese society in the 1980s and 90s. At the time, in particular in 1997, drug addiction was considered the country's main social problem according to the Euro Barometer survey [35]. As a result, a new policy on drugs was put into practice. First of all, Portugal assumed that application of the rules of law alone was an insufficient measure against drug addiction problems, and it became the first European country to officially abolish all criminal penalties for the personal possession of drugs. To simplify, drugs were 'decriminalized', but not 'legalized'. According to the legal framework of the Portuguese drug law, drug trafficking is considered a violent crime and a drug addict a patient who needs treatment. The new "drug action plan" privileged drug addiction in the health domain rather than legal-police intervention: jail was replaced by an offer of therapy [16].

Portugal started to gradually implement a humanitarian and pragmatic perspective to help people refrain from drug consumption and related addictions. Like other reports [9, 16, 35], a recent research study in Portugal has demonstrated that the clinical "reality" of heroin addiction has changed by being allowed to take a more positive direction. Comparing two periods of treatment admissions, classifiable as pre- and post-drug policy reform (1992-1999 and 2002-2013, respectively), the study results showed that treatment demand declined by 37%, whereas treatment engagement increased by 94% (due to bet-

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ter compliance); drug injection has decreased and heroin users are choosing to smoke heroin rather than injecting it. HIV infection decreased, too [30]. Apart from the new drug policies and other social norms, there are many other factors that might explain these changes. There have, for instance, been reductions in the prices of most substances, particularly heroin; for instance, the reported average price of 1 gram of heroin decreased from 50.27 Euros in 2001 to 33.25 Euros in 2008. Such price reductions appear to point to two phenomena: increased supply and reduced demand [16].

Currently, opiate stabilization programmes with methadone or buprenorphine are a widely used form of pharmacological treatment, showing effective results in heroin dependence trials [37]. Indeed, the introduction of methadone in the early 1990s as a treatment of choice was a major achievement in the addiction field. It enables a person who formerly engaged in often life-threatening heroin-seeking behaviour to be treated with a medication that is fully compatible with normal functioning. It keeps patients in treatment, while decreasing heroin use and related crime and health problems [20, 24]. However, despite evidence supporting the benefits of treatments – in particular, methadone maintenance treatment (MMT) – we now know from studies and clinical practice that heroin addiction is certainly a long-term disease, with what are assumed to be persistent consequences in terms of morbidity and premature mortality [13, 15]. Several studies have confirmed the high mortality of heroin addicts even after enrolment in MMT [31]. Moreover, other studies have shown that the mortality rate rises during the period following the moment when the patient leaves MMT, compared with that of opiate abusers who stay in treatment [12, 39]. Generally, accidental drug overdose and acquired immunodeficiency syndrome (AIDS) were the primary causes of death across heroin addiction cohorts [7]. Other mortality risks are trauma, heart, liver and infectious diseases. Increasing risk of death for older users by exacerbation of a pre-existing medical condition has also been suggested [5, 23]. Suicide is an outcome that makes an important contribution to the figures for overall excess mortality among heroin users, especially women [19].

Though mortality risks fall during MMT, they may increase again if the user stops treatment and resumes illegal opioid use, particularly if this resumption takes the form of heroin use by injection [17]. A study conducted by Sørensen et al, in 2005 [38], concluded that people who had achieved stable abstinence from injecting narcotics use were at lower risk of premature death than people with continued drug use.

In that sense, long-term follow-up studies play an essential role in facilitating and monitoring the potentially unstable course of heroin addiction [27, 36]. On that basis, in order to evaluate our cohort of heroin-addicted patients and understand the outcomes of treatment [30], the present follow-up analysis has aimed to explore mortality rates and related causes of death, together with current alcohol and drug use.

2. Methods

Correlational and comparative methods were used to assess the study objectives. Data were collected from the Addiction Unit of the Mental Health and Psychiatric Service of Santa Maria University Hospital in Lisbon. All patients were recruited from the therapeutic programme centre. Inclusion depended on meeting the criterion of a ‘primary’ diagnosis of heroin dependence. In DSM the “primary” drug is defined as the drug that causes the patient the most problems at the start of treatment. This is usually based on the request made by patients and/or on the diagnosis made by a therapist (commonly using standard instruments such as the Diagnostic and Statistical Manual of Mental Disorders - DSM) [2]. Our treatment unit has the philosophy of a "high-threshold programme”, which requires the patient to accept a certain level of control and counselling. The standardized outpatient treatment protocol, generally based on a contingency management programme, combines a pharmacological and a psychosocial intervention. In pharmacological terms, the addiction unit offers an opiate stabilization programme (methadone or buprenorphine) as the treatment of choice for people who are heroin-dependent. The main psychological treatment modality is group psychotherapy (weekly; 1 hour) and constitutes the core of the rehabilitation programme. Building a new drug-free lifestyle is the main psychotherapeutic goal of the programme. Flexibility and vigilance are important features of our unit. We facilitate patient entry into treatment by avoiding waiting times, we do not specifically fix a maximum dose limit for maintenance treatment, and patients can remain in our unit as long as they want [28, 29].

In order to evaluate the outcomes of treatment, we considered the cohort sample of heroin treatment-seeking patients from 1992 to 2013 that completed the clinical protocol (N= 627 patients). For a more detailed overview of the sample of 627 heroin-de-

pendent patients, please see Pombo and Costa (2016) [30].

To examine the heroin addiction profile, patients were assessed on their use of drugs, sociodemographic and clinical characteristics, family history and drug-related lifestyle, with an abridgement of the European version of the Addiction Severity Index (Europ-ASI). This semi-structured interview had been used in earlier reports [28, 29, 30]. These data were collected at each patient's admission to the treatment unit by trained psychiatrics and psychologists (time 0).

Exclusion criteria were patients younger than 18 years of age, patients that met the criteria for "primary" cannabis or cocaine dependence (other drugs), schizophrenia and/or other psychotic disorders, state of alcoholic intoxication (or intoxication with other substances) during assessment and marked cognitive deficit or mental retardation.

2.1. Follow-up procedure

In order to implement an outcome monitoring procedure, we conducted a telephone post-treatment follow-up interview, using a feasible and validated low-budget method that had been designed to evaluate outcomes after treatment [26]. Telephone interviews were carried out by our staff nurses from June 2014 through February 2015. Main outcome measures were: survival, cause of death, alcohol and drug use in the last month and professional status. Deaths were assigned to the category of being HIV-related if the patient died from an AIDS-defining disease: opportunistic infection, Kaposi sarcoma, HIV-associated lymphoma, AIDS dementia or HIV wasting [18]. In cases of death, information about the patient was collected from collaterals. Subjects were given a guarantee that all personal information would be treated as rigorously confidential. Point prevalence was used to determine the mortality rate by measuring the number of deaths occurring in the 22-year follow-up period, divided by the number of people tracked during that period. This survival monitoring procedure was used to discriminate between two subgroups in the study ("death" versus "not-death") in order to compare their profiles and outcomes.

2.1. Follow-up sample description

The sample of patients that were traced in the follow-up comprised 222 heroin-dependent patients (35.4%), 77.9% males (N=173) and 22.1% females (N=49), with a mean age at admission of 35.1 years and 7.6 years of education. Most of the patients in the sample were single (63.6%) and unemployed (53.2%).

2.2. Ethics

All the subjects involved in the study participated voluntarily and gave their informed consent. The study had been approved by the local Ethical Board of the Medical School of Lisbon University, and all the procedures described were conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983.

2.3. Data analysis

The normal distribution of the variables was confirmed by using the Kolmogorov-Smirnov test. Thus, considering normally distributed data, parametric methods were used to calculate the numerical relationships between variables. Comparisons between the two genders regarding baseline variables (sociodemographic and drug use data) were performed using chi-squared and Student t-tests. The Mann-Whitney U test was used to test group differences regarding the educational level, since the number of years of schooling completed did not present a normal distribution. To test for differences between respondents and non-respondents in terms of sociodemographic and pre-treatment clinical data and whether these characteristics were associated with treatment outcome, we used the chi-squared (χ^2), Mann-Whitney U (Z), Student t (F) tests and linear regression models adjusted for age, gender and school level. Logistic regression was interpreted in terms of odds ratios (OR). In the comparative analysis, all categorical variables were re-investigated using a logistic regression, where age, gender and school level included in the equation. All categorical variables were dummy coded (for example, females received code 0 and males code 1). Logistic regression was interpreted in terms of odds ratios (OR). For comparisons involving clinical continuous variables, a General Linear Model (GLM) was applied, incorporating age, gender and school level, which were used as covariates. Data were analysed using the Statistical Package for Social Sciences (SPSS-Version 20.0). Statistical significance was defined at $p<0.05$.

3. Results

3.1. Characteristics of the follow-up cohort

Considering gender differences, females were younger than males (F=0.2; p=0.06), but it should be noted that the results were only marginally significant. Concerning the 'primary' drug of abuse (heroin), patients reported more than one decade of consumption, more specifically 12.7 years (sd=6.4), with users preferring to smoke heroin (68.4%) rather than injecting it (31.6%). Almost all patients had used tobacco (98.4%), alcohol (98.4%), cannabis (94.4%) and cocaine (90.3%) at some point during their lifetime. Examining now age at onset of substance use, we can see that patients started to use tobacco (13.6), alcohol (14.7) and cannabis (15.8) at a mean age of 14-15 years, and cocaine (20.8) and heroin (20.3) much later, at a mean age of 20-21 years. An experience of needle sharing was reported by 34.6%, while HIV and hepatitis C infection were reported by 23.4% and 37.8%, respectively. About 25.1% reported lifetime history problematic alcohol use. At admission, 10.7% of the cases presented current problematic alcohol use. A previous history of delinquency and criminal behaviour was present in 37.4% and 39.6% of these cases, respectively.

3.2. Follow-up results

During the 22-year follow-up period, 30 (13.5%) heroin users died (24 were males and 6 females). The main causes of mortality were HIV-related (54.2%), followed by C hepatitis (8.3%), drug overdoses (8.3%) and other remaining causes, such as accidents, suicide or cancer (29.2%). The data were analysed in order to emphasize any differences between the two groups in the study: the follow-up group who were still alive, and the group of patients who had died. Comparative analysis showed that the patients who had died presented, at admission, significantly higher scores for HIV infection, intravenous drug use and sharing of needles, and more years of heroin and other drug consumption, when compared with the population of survivors. All statistical results are presented in table 1. Among the group of survivors, 17.4% reported that they had been using heroin and 15.5% cocaine in the previous 30 days. Problematic alcohol use (in the last 30 days) was reported in 11.9% of these cases. Statistical analysis did not show any significant differences between admission and follow-up results (χ^2=0.11; p=0.74). Considering professional situation, 37.1% were employed, 54.1% unemployed and 8.8% had retired. No gender differences were observed regarding either heroin (χ^2=0.7; p=0.38) or cocaine use (χ^2=0.3; p=0.57), or professional activity (χ^2=1.4; p=0.68). In any case, problematic alcohol use was only observed in male patients (χ^2=8.1; p<0.01).

4. Discussion

This study aimed to assess in a 22-year follow-up the vital and drug use status of a cohort of heroin-addicted patients that had been admitted for treatment during the period 1992-2013.

In Europe, chronic heroin use is generally linked to premature death [10]. Overall and cause-specific mortality can be considered a valid indicator of the health effects of drug addiction [4]. According to our long follow-up study, the estimated point prevalence of mortality was 13.5%, with the main cause of death connected to HIV/AIDS. These results were further confirmed by the comparative analyses, in which infection with HIV potentially transmitted through

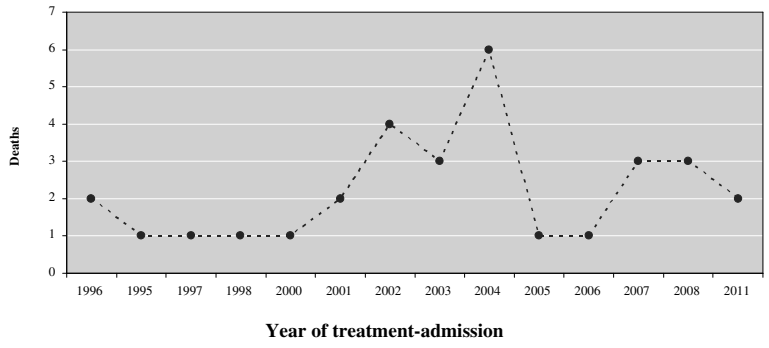

Figure 1. Deaths from all-causes according to years of treatment-admission

Table 1 - Demographic and clinical characteristics of mortality and non-mortality heroin addicted subjects

	Not-death 192(86.5%)	Death 30 (13.5%)	Statistics
Age at admission (M±SD)	35.1±7.1	34.9± 7.9	F =0.8 / p=0.85
Years of school attendance (M/SD)	7.8 / 3.3	7.4 / 2.9	Z= -1.4 p=0.20
Gender (%)			
Male	77.6	80.0	
Female	22.4	20.0	χ^2=0.8 / p=0.76
Occupational status (%)			
Employed	45.7	23.3	
Unemployed	49.5	76.7	
Retired	4.8	0.0	χ^2=8.0 / p=0.01
Onset of substance use			
Tobacco	13.6/3.3	13.1/3.7	F =0.6 / p=0.5
Alcohol	14.7/4.0	14.4/2.8	F =0.9 / p=0.8
Cannabis	15.8/3.3	15.7/2.9	F =0.1 / p=0.8
Cocaine	21.1/6.0	19.4/5.2	F =0.5 / p=0.2
Heroin	20.6/5.7	18.6/4.4	F =1.7 / p=0.1
Substance use habits			
Problematic alcohol use (lifetime)	24.0	33.3	OR=1.5 / p=0.4 (CI 95% 0.6 – 4.1)
Problematic alcohol use (current)	9.7	18.2	OR=1.4 / p=0.3 (CI 95% 0.5 – 4.3)
Tobacco	98.1	100.0	OR=0.0 / p=0.9 (CI 95% 0.0 – 0.0)
Cigarette number (day)	26.4/10.7	26.8/14.8	F =1.5 / p=0.9
Cannabis	94.7	92.3	OR=1.5 / p=0.6 (CI 95% 0.3 – 5.1)
Cocaine	89.3	96.3	OR=0.3 / p=0.26 (CI 95% 0.0 – 2.3)
Years of drug consumption	14.0/6.7	17.5/6.1	F =1.9 / p=0.04
Years of heroin consumption	12.3/6.4	15.5/6.1	F =1.6 / p=0.02
Previous drug treatments	3.0/2.4		F =3.5 / p=0.24
Drug overdoses	1.5/1.4	2.1/1.7	F =0.3 / p=0.3
Seroprevalence (%)			
HIV	20.3	43.3	OR=0.3 / p=0.05 (CI 95% 0.1 – 0.7)
C hepatitis	36.5	46.7	OR=0.6 / p=0.28 (CI 95% 0.3 – 1.4)
Mode of abuse (primary drug)			
Smoke	71.7	48.3	OR=0.4 / p=0.01 (CI 95% 0.1 – 0.8)
Intravenous	28.3	51.7	
Ever shared needles	29.5	65.4	OR=6.7 / p=0.01 (CI 95% 1.4 – 5.6)
Legal history			
Delinquency	37.5	36.7	OR=1.0 / p=0.8 (CI 95% 0.5 – 2.4)
Criminal behaviour	39.6	40.0	OR=0.9 / p=0.9 (CI 95% 0.5– 2.1)

Note: Values are expressed in percentages (%), means and *standard deviations* (M/*SD*). Groups were compared using Chi-Square (χ^2), *Mann*-Whitney U (Z), Student t (F) tests and linear regression models adjusted for age, gender and school level. Logistic regression was interpreted in terms of odds ratios (OR).

Legend: Seroprevalence for Hepatitis C Virus and Human Immunodeficiency Virus expressed the percentage of patients tested or confirmed in the medical records; Substance use habits defined the most important psychoactive substances that have been used during patients´ lifetime (expressed in percentage); Problematic alcohol use categorized lifelong *alcohol related problems;* Onset of substance use was defined as the age where a patient was most likely to *have started to use a specific psychoactive substance;* Years of drug consumption and years of heroin consumption consider the length of time of all substance *use and only of heroin use, respectively;* Previous drug treatments, was defined to assess whether the patients had previously been in some kind of "formal" treatment for drug abuse; Mode of abuse (primary drug) considers the behaviour associated with heroin consumption; and the Legal history refers to the percentage of patients that reported a delinquent behavior or/and criminal activity over the *lifetime.*

shared needles and syringes in the context of intravenous drug use were common markers of death. Our results are in accordance with findings from other cohorts of drug-using patients. For instance, a population-based, nationwide prospective cohort study of HIV-infected patients showed that HIV-positive patients infected due to a habit of injecting drugs had a substantially increased overall mortality compared with patients who had acquired their infection through other routes [18]. Among this population of injecting drug users, death could result from serious infections connected with AIDS, such as pneumonia, endocarditis or sepsis.

At treatment admission patients who had later died presented a longer drug-use career than that of the surviving patients. With respect to deaths related to drug use in Portugal, data from the Portuguese National Institute of Statistics point to approximately 10-30 deaths annually, marked by slight fluctuations over the years [35]. The pattern of deaths had apparently changed from being largely due to overdose in the early 1980s to predominantly AIDS-related in later years [32]. Our results corroborate several other reports across Europe that have consistently shown that the practice of injecting drugs is associated with a high risk of death, particularly from the complications of HIV infection and full-blown AIDS [13, 23, 34, 41]. A ten-year survival analysis of a cohort of 138 heroin addicts in Catalonia concluded that 41 of those addicts had died (30%) [34]. A previous study on drug-related mortality across eight European countries reported mortality rates ranging from 1 per 100 person-years in Dublin and London to 3.8 per 100 in Barcelona – rates that were 6-54 times higher than those expected in the general population. The lowest mortality rate was recorded in Lisbon; however, the authors concluded that this result may reflect problems arising from the coding/certification of deaths [5]. A follow-up study among users of drugs (heroin, cocaine, and/or amphetamines) in Amsterdam (n = 899; 1985–2002) noted that at least 27% of drug users had died within 20 years after starting regular drug use and that the prevalence of abstinence for at least 4 months from the above drugs and methadone was only 27% at 20 years since initiation [40]. At this point it should be pointed out that the task of comparing these types of studies is difficult because of the use of different study groups, methods, and calculations, as well differences between sample sizes, countries of origin, and the length of follow-up periods [4, 13].

Heroin addiction is a chronic relapsing condition [15], in which episodes of frequent use of the drug often alternate with episodes of abstinence [14, 32, 40]. Considering the main drug of abuse (heroin) in our follow-up assessment, 17.4% of participants were probably in a relapsing condition. The rate of current heroin use in the sample of survivors participating in our study is comparable with that of other long-term follow-up studies. For instance, two 33-year follow-up studies observed rates of 20.7% [15] and 20% [25] and recently, Jimenez-Treviño et al, in 2011 [13], in a 25-year follow-up study found a 22.6% rate of current heroin use in patients admitted to methadone treatment for the first time. In general, our findings support the conclusions of Termorshuizen et al, [40], who posit that the mortality rates and the prevalence of abstinence among patients who remained alive over the long term indicate that the concept of natural recovery or "maturing out" in reaching a drug-free state does not apply to a substantial portion of the addict population.

Although heroin users commonly present an unstable employment situation, psychosocial factors such as unemployment have received little attention among illicit drug users [42]. In our study, the experience of unemployment was frequent (53.2% at hospital admission), undesirably stable (54.1% at the 22-year follow-up) and found to be a significant indicator of a mortality effect (76.7% in the sample who died). According to previous reports [7, 19], unemployment may be a marker of poor social integration or of difficulties in obtaining access to and benefiting from available health services. Therefore, given that heroin users face a variety of obstacles in finding employment, possibly due to stigma, their drug-related lifestyle, inadequate education and skills, or health problems, our findings emphasize the need to centre the therapeutic focus on the psychosocial difficulties encountered in making the transition to employment.

Alcohol misuse in heroin addiction is a serious clinical problem [28, 29] – a phenotype typically seen as a conversion of what was, initially, essentially a form of opioid dependence into polytoxicomania and alcoholism [6]. Maremmani, et al. [22] argued that alcohol-abusing heroin addicts seem to suffer from a metabolically acquired stain, which derives from preconditioning opiate abuse, and later prompts either opiate- or alcohol-seeking behaviour in an addictive way. The authors call it a masked form of "heroinism". Even though some variations in the prevalence of alcohol abuse may occur, since different definitions of problematic alcohol use are employed and the populations studied are heterogeneous, our baseline and

follow-up data confirm that around 10% of the heroin addicted population presented a drinking problem in the previous 30 days. Alcohol-related problems were more prevalent among men than women [3]. The stable course of alcohol abuse in drug use populations has been documented in the previous literature [15, 21]. For instance, a study conducted by Fairbank et al. [11], who compared the consumption of six substances (cocaine, amphetamines, illegal methadone, marijuana, tranquilizers and chronic alcohol use) in a 1-year follow-up, observed the generally lower levels of substance use in the follow-up assessment, except for alcohol use, which remained stable during the preadmission and follow-up years. It has also been shown that methadone-using patients who drink excessively are at a significantly greater risk of getting cirrhosis, esophageal varices, or other medical complications, and run a high risk of death [1]. Higher death rates and medical illness have been reported among alcohol-using patients in methadone treatment [33]. Even though higher percentages of current and lifetime problematic alcohol use (18.2 vs. 9.7% and 33.3 vs. 24.0%, respectively) were observed in the population of those who died, when compared with the cohort who lived, results were not statistically significant. In conclusion, our study results on alcohol use clearly prompt the recommendation that drug treatment units should implement a clear policy for treating alcohol-related problems. Because patients who drink heavily are those who are most vulnerable, and also those whose predicament is most likely to remain undetected even in treatment settings, clinicians should carefully screen all patients for alcohol abuse and offer appropriate combined pharmacological and psychosocial treatment [8].

Limitations

The results reported here should be considered in the light of certain limitations. The first is the quantity of data that are missing from the follow-up analysis. Patient-tracking problems emerged as the major reason for non-response, but this particular issue is inevitable in the present type of research, mainly because of the long follow-up time and the unstable lifestyle of these patients, for instance, in terms of keeping track of telephone numbers or home addresses [26]. Secondly, there is the lack of information regarding psychiatric comorbidity. Thirdly, we exclusively recruited heroin-addicted subjects from a treatment setting that probably differs from that of patients who do not enter treatment. We should therefore be extremely cautious about extending our results to other populations. Furthermore, although it is considered by definition that patients 'voluntarily' seek help in our drug dependence unit, we have to ponder in the light of our national drug policy that some patients may be assigned to seeking treatment by recommendation of the Commissions for the Dissuasion of Drug Abuse (cases of illegal drug use), a committee consisting of three people nominated by the Ministries of Health and Justice. Fourthly, given the importance of immune system disorders among the causes of death within the cohort, it is quite possible that HIV infection was such a powerful predictor of death that it swamped the rest of the predictive factors [34]. Fifthly, causes of death were not confirmed by the national mortality database, but they were clearly confirmed by the hospital records. Lastly, although there are key causes of death directly attributable to problematic drug use, heroin-addicted patients can die from many other 'ordinary' causes.

5. Conclusions

In general, our results agree with other positive findings achieved in our previous study [30]. Our 22-year follow-up study in treatment-seeking patients who had a history of heroin addiction showed a relatively low rate of premature death (13.5%). Among those who died, we must highlight the impact that HIV infection (AIDS) has had on the mortality rate of the population of heroin addicts since the early nineties, mainly due to drug use by injection. Although most of these patients reported a stable, drug-free status two decades later, we must note the undesirably stable prevalence of alcohol-related problems (around 10%).

In sum, our results clearly confirm the assumption that, by limiting the negative impact of intravenous drug use (and of what is, plausibly, the consequent transmission of HIV), we will be able to significantly improve the overall levels of health of the population. The prevalence of drug and alcohol use in the sample suggests the need for constant monitoring of our elderly patients.

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Conflict of interest

All authors have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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Methadone versus torture: The perspective of the European Court of Human Rights

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Summary

For the first time, the European Court of Human Rights in Strasbourg has addressed the issue of whether persons with a heroin dependence syndrome in custodial settings are entitled to receive opioid agonist treatment (OAT). The court relied on Article 3 of the European Convention on Human Rights, which prohibits torture as well as inhuman or degrading treatment. It concluded that member states of the Council of Europe that refuse access to OAT have the burden of proving that an alternative medical approach would, in the case of an individual patient, be as effective as OAT. Such proof needs to be based on an independent medical opinion. This paper discusses the scope and limitations of the European Court of Human Rights' judgment.

Key Words: Methadone; opioid agonist treatment; prisons; international laws

In the field of psychoactive substance use disorders, few medications have demonstrated their efficacy in the long-term treatment of these disorders as well as agonist medications for opioid dependence syndrome [24]. Indeed, in 2005, both methadone and buprenorphine were added to the WHO model list of essential medicines [23]. ICESCR (International Covenant on Economic, Social and Cultural Rights) considers that any failure to make these two medicines available is a serious breach of the right to enjoy the highest attainable standard of health [9, 18]. Yet, the medicinal status of methadone or buprenorphine remains ambiguous, as they are still subject to special regimes related to the international control of 'narcotic' substances, in most countries [21]. Historically, treatments using opioid agonist medications were the subjects of controversy, as were "risk and harm reduction" policies and measures, e.g., needle exchanges. The still widespread designation "substitution treatments" (suggesting the replacement of a 'street drug' by a 'state drug') illustrates this ambiguity [20]. In fact, the special regimes mentioned above are accompanied by various restrictions on medical practice, including the need for physicians to hold a State permit, requirements regarding eligible patients, the selection of prescribed opioids and their method of delivery, together with conditions related to professionals and healthcare availability [1, 17]. These restrictions are applied in many jurisdictions. Often they impair or sometimes even block access to these medications [19]. Furthermore, people deprived of liberty are particularly likely to encounter severe restrictions [21].

Recently, the European Court of Human Rights (from now on, more concisely: the Court) in Stras-

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bourg explained why access to methadone treatment in prison can indeed constitute a State duty and responsibility. This paper discusses the scope and limitations of this judgment.

1. Mr. Wenner versus Germany, 1st September 2016

In its ruling of September 1, 2016, the Court convincingly explained why the practice of prescribing methadone to detainees, paradoxical as it may seem to some, can constitute a legal obligation of Member States of the Council of Europe. Accordingly, refusal to grant access can constitute a breach of Article 3 of the European Convention on Human Rights (ECHR), which prohibits torture as well as inhuman or degrading treatment.

In this affair, the Court had to decide whether the refusal by the German authorities and the German courts to grant methadone access to an inmate diagnosed with long-standing heroin dependence syndrome was in compliance with the State's obligations under Article 3. The appellant, Mr. Wenner, born in 1955, had been using heroin for 17 years. For more than 16 years (1991-2008), he had benefited from an overall successful treatment with methadone. Sentenced to six years in prison for "drug trafficking", he had asked to continue his methadone-based treatment in prison. The Bavarian prison authorities and courts refused, ordering instead a treatment based solely on abstinence. Abstinence proved to be a failure, and Mr. Wenner continued to consume a range of psychoactive substances available through the prison's black market. He continued to request methadone; as the best alternative, he demanded that his health status and need for treatment be evaluated by external medical specialists. Despite his efforts and appeals, his requests were rejected. It was only when he was released, at the end of 2014, that Mr. Wenner resumed his methadone treatment.

2. States have a particular duty to ensure the health of their detainees

Mr. Wenner brought his complaint before the Court, arguing that the two refusals that he had sustained violated Article 3 of the ECHR. Not only is it forbidden for each member State in the Council of Europe to inflict degrading treatment, so much so that every State is actually required to take positive measures to avoid causing suffering. Yet, not all painful treatments are viewed as being sufficiently severe to be prohibited by Article 3. Determining whether a treatment is 'sufficiently' degrading will depend upon the circumstances of each case, including the age and health status of each individual involved. With regard to detainees, the State responsible for their incarceration has a special duty to safeguard their health and to ensure that detention conditions, including health care services, remain adequate.

In its judgment of September 2016, the Court held that it did not have to decide whether methadone-based treatments (commonly referred to as 'opioid agonist treatment, or OAT'),' or historically as an "opioid substitution treatment" (otherwise OST), are the most appropriate of all for the treatment of heroin dependence syndrome. Instead, it chose to focus on Mr. Wenner's second grievance, i.e. the authorities' duty to assess the therapeutic need for methadone treatment based on the expert opinion of independent medical specialists. On this point, the Court favoured Mr. Wenner, and unanimously condemned Germany. Even if the Court only ruled on the need to resort to independent expert opinion, the grounds for its judgment strongly suggest that a State must provide OAT to any detainee who meets the treatment's criteria foreseen for those who wish to undertake it. This conclusion holds at least in the following circumstances: The detainee has been diagnosed as suffering from long-standing heroin dependence syndrome; previous treatments, including those whose direct objective was abstinence, have failed; doctors who assessed the patient recognize that abstinence-based therapeutic options hold little chance of success; and without OAT, the patient undergoes mental and physical suffering.

Two points should be highlighted at this point. Firstly, the State's obligation to provide methadone does not end once the inmate has undergone the treatment in detention. Heroin dependence syndrome is recognized as a chronic disease, and the fact that the patient is no longer in the acute phase of withdrawal does not mean that he is definitely cured and no longer needs methadone. Secondly, it is the States' responsibility to prove that the treatment being offered in prison is appropriate; the Court wrote: "having regard to the vulnerability of applicants in detention, it is for the Government to provide credible and convincing evidence showing that the applicant concerned had received comprehensive and adequate medical care in detention".

An interesting question is what led the Court to avoid the first issue – does OAT constitute the only

adequate treatment? – and to focus instead on the second issue, namely, the need for independent expertise to determine the most appropriate treatment.

3. The principle of equivalence

The starting point for the Court's reasoning is the principle of equivalence. It is accepted under international law that a person deprived of liberty is entitled, in principle, to the same level of healthcare as a free person. Detention is not a valid reason for providing less extensive or lower-quality care. If OAT were to be regarded as the standard treatment for "ordinary" patients, the same should be true for those in prison. On this point, the Court took the opportunity to refer to a study [25] – there are actually several [6, 8, 13, 24] – endorsed by the German State, which concluded that: "long-term substitution treatment [with methadone] had proved effective in that the primary aims of that treatment (that is, continuity of treatment, survival, reduction of substance consumption, stabilization of comorbidity and securing social participation) were attained". Conversely, there is strong evidence that an opioid abstinence regime without adjunct medicines almost always fails, while often leading to lethal intoxications when patients revert to consumption [3, 15, 24]. In addition, this study states that OAT should be implemented as a long term, or sometimes even permanent, treatment. It should therefore not be interrupted prematurely, particularly for a period of incarceration. The Court also took the opportunity to refer to the statistics on the availability of OAT in Council of Europe member countries: In 2012, 41 of the 47 members offered this therapeutic option, of which 30 (out of 47) offered the treatment equally to detained individuals.

At this point, one might predict that the Court would conclude that OAT is not only “standard”, but also the only treatment to be envisaged. The Court, however, chose not to go so far, leaving the State with a margin of latitude to decide on a case-by-case basis. For some opioid-dependent patients, especially those who are highly motivated, a programme of abstinence may be attempted. Thus, the State retains the option of proving that, in the case of a specific patient, medical experts agree that abstinence-based treatment could safely treat the opioid dependence syndrome.

This step in the Court's reasoning deserves further comment. Abstinence-based treatment can only be implemented with the patient's free and informed consent, especially because only motivated patients make good candidates for such an approach. In other words, if the detainee is not motivated by rapid substance use cessation, such a measure seems a priori devoid of any chance of success. Consequently, in the case of Mr. Wenner, who had decided to reject forced abstinence, the Court could have answered the first question by saying that abstinence-based treatment was in no way appropriate for him, leaving OAT as the only remaining effective and available treatment.

What, then, can explain this reluctance of the Court? The Court often prefers not to encroach on the sphere of doctors’ competence. When the question requires technical knowledge, particularly the assessment of various medical options under a risk-benefit approach, the Court considers that experts should be allowed to decide first. This also led the Court to focus on Mr. Wenner's second grievance (the need for one or more independent experts to assess his medical situation). In a rather subtle way, the court sends the following message: since it is up to the States to prove that prison healthcare is adequate, they must also accept responsibility for obtaining independent medical expertise. This is especially true when they seek to (lawfully) impose a treatment different from the one commonly accepted by the medical community and requested by the patient.

4. A global health issue

According to The Global State of Harm Reduction (2016), global access to OAT has improved since 2014; it is actually being proposed in prisons within 52 countries [21] (see Figure 1). However, this progress should not obscure a more complex reality: the implementation of OAT in detention facilities is subject to considerable disparity and problematic medical care implementation, such as delivery of opioid medication directly by prison custody staff due to lack of nursing staff [3]. When OAT is being proposed, the extent of coverage often remains limited, at least in the few countries where such data are available. As an example, only four of the fifty US states reported numbers on OAT’s availability in prison, while studies indicate that about 90% of people currently receiving OAT in the USA would have their treatment stopped in a detention context [21]. Only a few countries are deemed to have an optimal availability rate; this is true for Switzerland, where some prisons even propose medical prescription of heroin for patients for whom OAT has consistently failed. However, the Swiss Epidemics Act, in force since 1st January 2016, obliges institutions to make sterile injecting equipment available for detainees [22], even though

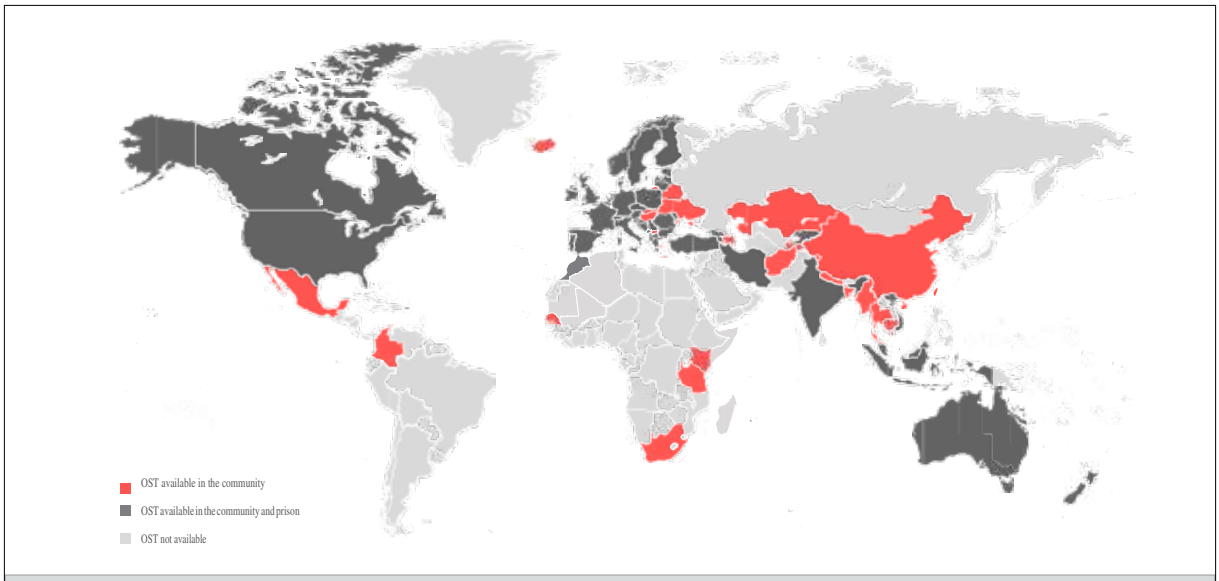

Figure 1. Global access to OAT

only 15 out of 110 prisons have yet implemented this provision [4]. Thus, even in countries that have in place regulatory provisions supporting the principle of equivalence of care, the limited effective availability of treatment calls for a rigorous evaluation effort. OAT and risk reduction measures for prisons remain a considerable public health issue, and subsequently an issue for the improvement of monitoring systems regarding public policy on psychoactive substances.

5. OAT improves patients' physical and mental health

The ECHR's judgment establishes that States must guarantee the availability of OAT for most people with dependence, since it has proved to be the best scientifically identified and tested solution to date. OAT helps patients to stabilize their medical and social status by improving their physical and mental health. It reduces the risk of lethal intoxication, while suppressing the hedonic stimulating effects of additional doses of heroin. By removing the tensions and the dangers associated with obtaining an illegally produced (and sometimes tainted) substance, it allows patients to stay away from the 'drug scene', thus precluding criminal violations and therefore prison. OAT reduces crime related to controlled substances, and therefore reduces the associated judicial and prison costs. It also maintains patients' social ties with their surrounding network and, in the best case, allows them to live without any negative consequences regarding family, social and professional relationships. In terms of public health, OAT minimizes the transmission of infectious diseases spread by sharing needles for heroin injection: it significantly reduces the rate of HIV and, similarly, hepatitis B and C transmission.

What is true for the general population applies pari passu to detained individuals. First, methadone delivery prevents the avoidable withdrawal-associated suffering, without endangering the health of the patient as long as it is prescribed lege artis. It is therefore the best medical and ethical solution. For as long as heroin and other controlled substances circulate in prison [11], it is better – both for the individual's health and for public health – that the inmates receive treatment that maximizes their mental and physical state. Lastly, as detainees eventually complete their prison sentences, it is preferable to release them in a stable mental and physical state under OAT – rather than as a consumer in constant need of heroin and at high risk of a lethal intoxication [2, 7, 10, 12, 16].

6. A significant step forward

In summary, the Court's judgment represents a significant step forward in ensuring access to OAT in the Council of Europe's 47 Member States, and possibly beyond. From a legal standpoint, the Court found an elegant answer to the question why access to methadone treatment in prison can indeed constitute a State's duty and responsibility, even though, on an institutional level, it leaves follow some substantial issues concerning the practical application of the equivalence of care principle for other harm reduction and health promotion measures. The key message re-

mains: OAT is currently the most pragmatic therapeutic option – the best tested and the most effective available – both in prisons and, more broadly, in society. For the State, to deny it to an opioid-dependent person is, indeed, a form of inhuman and degrading treatment prohibited by article 3 of the European Convention on Human Rights.

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Footnotes

a) the judgment, reference 62303/13, is available from the Court's data base at: http://hudoc echr.coe.int/
b) convention for the Protection of Human Rights and Fundamental Freedoms concluded in Rome, 4th November 1950; these texts can be accessed at: http://www.echr.coe.int/documents/convention_eng.pdf
c) see Point 58 of the judgment.
d) European Committee for the Prevention of Torture

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e) see Point 31 of the judgment.
f) see Points 36, 37, and 64 of the judgment, which refer to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Prisons and drug abuse in Europe: the problem and responses (2012). Cfr. la voce n. 3 della bibliografia: Publications Office of the European Union, Luxembourg.

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HW is a member of the Committee for the Prevention of Torture (CPT) of the Council of Europe in the name of Switzerland and also member of the Central Ethics Committee of the Swiss Academy of Medical Sciences. He declares no conflicts of interest.

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Characteristics of methadone-related overdose deaths and comparisons between those dying on and off opioid agonist treatment (OAT): A national cohort study.

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Summary

Background: Opioid users, particularly those with a history of injecting and dependence, have a high risk of fatal poly-substance and methadone-related overdose. **Aim:** To describe characteristics of methadone-related overdose deaths and assess if differences exist between those dying on and off opioid agonist treatment (OAT). **Methods:** A descriptive study of all persons dying of drug overdose involving methadone on the Irish National Drug Related Deaths Index (NDRDI) in 2012 and 2013. **Results:** A total of 182 methadone-implicated deaths were recorded. 78% (n=142) were male; with a mean age of 36 years. Of the cohort, 61% (n=111) were not in receipt of opiate agonist treatment (OAT) at the time of death, 15.9% (n=29) had a previous history of non-fatal overdose and 24.7% (n=45) a history of alcohol dependence. Analysis and interpretations are limited by incomplete data on other characteristics but where available show that 89% (n=73) were injecting drug users, with 57.8% (n=26) injecting drugs at the time of death. History of mental illness was recorded in 96.3% (n=77) of cases, with 94.7% (n=107) having history of substance dependency treatment. Polysubstances were implicated in 86.8% (n=158) of deaths. The majority died in a private dwelling (74.7% n= 127) and were not alone 67.4% (n=114). **Conclusions:** Methadone-related fatal overdose is a significant cause of death in young Irish, who share many characteristics with other drug-related deaths. Improved monitoring, risk assessment and OAT retention strategies is warranted to inform national drug overdose plans and overdose prevention.

Key Words: Overdose; methadone; opioid agonist treatment (OAT)

1. Introduction

Opioid users, especially those with a serious opiate addiction and those who inject drugs, are at risk of overdose deaths [4, 11, 18, 22, 25]. Efforts to compare accidental drug overdoses across countries are problematic but there is evidence of increasing deaths from prescription opioids and decreasing deaths from illicit drug use [17]. Enhanced and robust surveillance and monitoring systems are necessary to reduce drug-related deaths among drug users on Opioid Agonist Treatment (OAT). With the prevalence of methadone-related overdose deaths increasing globally, concerns arise regarding the diversion of OAT drugs, in particular black market methadone [4, 16]. Recent data in the UK underscored that half of drug-related deaths were among people who used opiates and had no recent contact with drug services [21]. Public Health England commented on various contributors to this increased trend in 2016, which included variations in the purity and availability of street opiates, patterns of poly-substance use, use of new psychoactive substances, and the increasing age and poor physical health of drug users [24].

Whilst OAT, particularly methadone pharmacotherapy, is shown to reduce mortality among individuals with problem opioid use [3, 7, 10, 23, 25, 26], accidental overdose deaths often occur after a

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reduction in opioid tolerance following a period of abstinence, for example when exiting OAT, recently detoxified or prison discharge [6,10, 20, 26]. Cousins et al. [4] observed that primary care methadone treatment patients were almost four times more likely to die during periods *'off treatment'*, in those initial high risk few weeks after leaving treatment. Definitions of *'off treatment'* generally mean *'not receiving a methadone prescription for three days since the end of the previous prescription'* [4]. Mortality risks for methadone patients include having a history of alcohol misuse [13], consuming a methadone dose below 60mg [15], Human Immunodeficiency Virus (HIV) infection [14], medical co-morbidity [19] and history of psychiatric illness with co-prescription of benzodiazepines [13,19]. Factors reducing overdose risks centre on living with a partner, having a younger age, not abusing benzodiazepines and remaining in treatment [2, 13, 23].

In Ireland (study location), the Irish National Drug-Related Deaths Index (NDRDI) report for the period 2004-2013 on deaths from poisoning and deaths among drug users. The most recent report showed that alcohol was implicated in 1 out of 3 poisoning deaths in 2013, poly-substance poisoning in 60% of deaths, and an increase in heroin-related deaths [12]. Patterns of benzodiazepine consumption and use of other drugs whilst on methadone treatment are of increasing concern in Ireland [4, 9]. Irish patients on methadone identified as having significant risk of fatal overdose are those patients with medical issues such as HIV and Hepatitis C Virus (HCV) infection, a history of imprisonment and homelessness. Another Irish study identified a history of imprisonment as being an increased risk of death while on methadone treatment [26].

In 1998, the Methadone Treatment Protocol (MTP) was introduced in Ireland [8] which resulted in a change to how methadone could be prescribed and dispensed. These new national regulations required that all patients being prescribed methadone are registered on a central treatment list (CTL). When patients are no longer in receipt of methadone through either completion of a treatment episode or defaulting from treatment, the patient's name is removed from the register after one month. It is therefore possible to identify which methadone-implicated deaths relate to people registered on the CTL and those not registered. Our study aimed to describe the characteristics of methadone-related overdose deaths in Ireland over a 24-month period and assess if differences existed between those dying when registered and not registered for OAT. We also considered that there may have been identifiable differences between those who died and were not on treatment at the time of death and those who died and were in receipt of treatment at the time of death.

2. Methods

The National Drug Related Deaths Index (NDRDI) in Ireland is an epidemiological database which records all deaths by drug and/or alcohol poisoning, deaths among drug users and deaths among those who are alcohol dependent. To ensure comprehensiveness, data for the NDRDI are collected from four sources, the Coroner Service, the Hospital In-Patients Enquiry Scheme (HIPE), the Central Treatment List (CTL) and the General Mortality Register (GMR) through the Central Statistics Office. The Coroner Service establishes the cause of death in cases of sudden or unexpected death and will, following an inquest, determine the cause of violent or unnatural deaths including those caused by drug and alcohol poisoning. Data from 48 coroners districts nationally are included in the NDRDI. HIPE is a computer-based patient information system which collects medical data on discharges and deaths in acute general hospitals in Ireland. Sixty hospitals, accounting for 95% of all hospitals nationally, enter data on this register and where appropriate this data is automatically entered onto the NDRDI. The CTL is a statutory register of all patients receiving methadone treatment in Ireland. This register provides data for those on methadone treatment at the time of death which is sent electronically to the NDRDI by CTL staff. The GMR formally records, categorises and codes all notified deaths in Ireland with only one underlying cause and one external cause recorded for each death. This data are sent electronically to the NDRDI. Cases from the different data sources are cross-matched to avoid duplication and a comprehensive set of variables is collected on each unique drug-related death.

The NDRDI categorises drug-related deaths into poisonings and non-poisonings. Poisonings or fatal overdoses are defined as deaths in individuals due to the toxic effects of the consumption of drug(s) and/or other substance(s) and do not include adverse reactions to prescribed medications. For this study, all methadone-related poisoning deaths were extracted from the NDRDI for 2012 and 2013. Anonymised data on the following characteristics was collected on the full study cohort (n = 182); age, gender, place of residence, registered for methadone treatment, drug

Table 1: Demographics

	n	%
Year		
2012	89	49.9
2013	93	51.1
Sex		
Male	142	78.0
Female	40	22.0
Age Group		
<25	24	13.2
25-34	74	40.6
35-44	47	39.1
45+	37	20.3
Place of residence		
Dublin city/county	128	70.3
Other city area	12	6.6
Other areas	42	23.1
Location of death		
Private dwelling	127	74.7
Homeless accommodation	23	12.6
Public place	9	4.9
Public building	5	2.7
Other	6	3.3
Present at time of death		
Alone	55	32.5
Partner/children	27	16.0
Family	37	21.9
Friends	24	14.2
Other	26	15.4
Known to be registered on OAT at time of death	71	39.0

and alcohol dependence, history of overdose, history of blood borne viruses, ante- and post-mortem toxicology. Incomplete data was available on the following characteristics, location at time of death (n=170), presence of others at fatal overdose (n=169), history of mental illness (n=80), history of injecting (n=82), ever treated for substance dependency (n=113), injecting at time of death (n=45) and treated for drug problems at the time of death. (n=97). Descriptive statistics (frequencies, percentages) were used to summarise the characteristics of those dying of methadone-related poisonings. Statistical tests using SPSS included chi-squared tests, t-tests and p-values were used to assess differences in categorical data, with a significance level of 0.05. Multi-nominal logistic regression analysis was used to determine predictors for being on and off methadone treatment at the time of death.

3. Results

There were 182 poisoning deaths where methadone was implicated as a cause of death on the NDRDI over the two-year period 2012-2013. Of the 182 individuals included, over three quarters (78%, n=142) were male; the mean age was 36 years with the lower and upper quartiles being 28.75 and 41 years, and 70.3% of the deceased were resident in Dublin city or county. The place of death was recorded for 170 of the cases with the majority (74.7%, n= 127) dying in a private residence, 12.6% (n=23) in a homeless hostel, and 7.6% (n=14) dying in either a public place or building. Where recorded (n=169), in over two thirds (67.5%) of fatal overdoses there was a third-party present (Table 1).

The majority of the deceased were not registered for OAT at the time of death, 61% (n=111). One quarter 24.7% (n=45) of the individuals who died were known to have alcohol dependency and 15.9% (n=29) had a history of overdose in the past. Where recorded, the most common blood borne virus (BBV) infection in this cohort was HCV (23.6%), followed by HIV (6.6%). However history of BBV was not always available in the sources used by the NDRDI. For several characteristics, data was not available to the NDDRI from the available sources. For clarity, the denominators for these characteristics are included in brackets. Where data was available, 96.3% (77/80) had a known history of mental illness, 89% (73/82) of individuals were recorded as having a history of injecting drugs, with 57.8% (26/45) documented as

Table 2: Dependencies and Treatment History

	n	%
A. Mental Illness		
A1. Alcohol dependency mentioned	45(/182)	24.7
A2. History of mental illness	77 (/80)	96.3
A3. Ever treated for substance dependency	107 (/113)	94.7
B. Drug Use		
B1. Recorded history of overdose	29 (/182)	15.9
B2. History of injecting drugs	73 (/82)	89.0
B3. Injecting at time of death	26 (/45)	57.8
B4. Treated for drug problem at time of death	89 (/97)	91.8
C. Virology recorded		
C1. Hepatitis C	43 (/182)	23.6
C2. Hepatitis B/unspecified	7 (/182)	3.8
C3. HIV	12 (/182)	6.6

Table 3 Comparison between those on OAT and not on OAT

	Not registered on OAT at the time of death (n=111)	Registered on OAT at the time of death (n=71)	p-value
Mean age	34.22 (SD: 11.0)	38.99 (SD: 8.4)	*0.003
Sex Male Female	 74.6 (89/111) 25.4 (22/111)	 80.2 (53/71) 19.8 (18/71)	0.463
Place of residence Dublin city/county Other city area Other areas	 63.1 (70/111) 6.3 (7/111) 30.6 (34/111)	 81.6 (58/71) 7.0 (5/71) 11.4 (8/71)	*0.024
Alcohol dependency mentioned	27.0 (30/111)	21.1	0.386
Ever Treated for drug dependency	73.1 (19/26)	98.6	*<0.01
Ever Injected	79.5 (31/39)	97.7	*0.012
Injecting at time of death	55.0 (11/20)	60.0	0.220
History of mental illness	97.7 (43/44)	94.4	0.585
Ever treated for substance dependency	85.7 (36/42)	100	*0.002
Hepatitis C	16.2 (18/111)	35.2	*0.004
HIV	4.5 (5/111)	9.9	0.220
Polydrug poisoning	91.9 102/111)	87.3	0.322

Continuous variables assessed by independent T-test; Categorical variables assessed by Chi-square. *Variables deemed statistically significant, p<0.05

injecting drugs at the time of their death. The majority, 94.7% (107/113), had been treated for substance dependency at some stage, with 91.8% (89/97) being treated for problem drug use at the time of death (Table 2).

Table 3 compares those registered for OAT at the time of death to those who were registered for OAT. When comparing the available data for those who were registered for OAT at their time of death, statistically significant differences were found in: mean age (p=0.003), place of residency (p=0.024), ever treated for drug dependency (p=0.000) and Hepatitis C (p=0.003); however, none of these remained significant on the multivariate logistic regression, except those who had been recorded as ever treated for drug dependency.

Ante- and/or post-mortem toxicology results were available for 171 of cases, with the majority, 86.8% (n=158), of the deaths being poly-substance related (including opiates, such as heroin and methadone). Methadone alone was found in 9% (n=16) of cases and 3.5% (n=6) were found to have opiates alone. A wide range of drugs were found in the toxicology results. Significant differences were noted regarding those registered and non-registered CTL individuals in terms of their use of prescribed medication. Individuals not registered on the CTL were statistically more likely to be using non-prescribed methadone (p<0.01), diazepam (p=0.02) and mirtazapine (p=0.02) at the time of death. (Table 4).

4. Discussion

This study reports on a particular cohort of drug-related deaths in Ireland where methadone has been implicated in the death, and builds on earlier studies conducted using NDRDI data [12]. There is growing concern about drug-related deaths in many jurisdictions [1, 6, 17]. The role that prescribed and diverted methadone plays in these deaths has been documented [4, 16] but there is a paucity of research on this unique cohort [13]. The study examined in greater detail the characteristics of those who died where methadone was implicated in the cause of death and to examine if there were differences in the characteristics of patients who were registered for OAT and those who were not.

This study shows that methadone-related deaths account for a significant number of deaths in young men in Ireland. Over a two-year period, 142 men with a mean age of 36 years died in Ireland from what is a preventable cause of death. Despite the numbers, these deaths do not get the same attention, for example as road traffic deaths or deaths by suicide. Of note is the number of very young people (< 25 years) (n= 24) in this cohort. With an aging opiate using population, this finding was unexpected. Comparative analysis between those on and off treatment showed those

Table 4 – Toxicology Results

Substance	N	% On OAT	% Not on OAT	% OAT not prescribed	% Non OAT not prescribed	p-value
Methadone	171	40.9	59.1	34.3	91.1	*<0.01
Heroin	60	46.7	53.3	100.0	100.0	-
Hypnotics (Non BZO)	84	44.0	56.0	78.4	87.2	0.378
Diazepam	131	39.7	60.3	71.2	87.3	*0.025
Alcohol	61	34.4	65.6	100.0	100.0	-
Flurazepam	52	55.8	44.2	69.0	91.3	0.086
Alprazolam	31	48.4	51.6	93.3	100.0	0.484
Amitryptlline	16	81.3	18.8	61.5	100.0	0.509
Cocaine	21	33.3	66.7	100.0	100.0	-
Mirtazapine	54	46.3	53.7	64.0	89.7	*0.046
Olanzapine	23	60.9	39.1	57.1	55.6	1.00
Tramadol	15	33.3	66.7	80.0	70.0	1.00
Citalopram	14	35.7	64.3	100.0	66.7	0.258

Continuous variables assessed by independent T-test; Categorical variables assessed by Chi-square. *Variables deemed statistically significant, p<0.05.

dying off treatment were younger than those on treatment. Being on OAT may account for this finding, but consideration should also be given to the possibility that this group contains a younger cohort of less experienced drug users who had not yet come in contact with OAT. Further analysis of this younger cohort is necessary to determine their unique characteristics and inform specific overdose prevention to target this group.

This study showed that more people died off treatment (not registered for OAT) than in treatment (registered for OAT). Another Irish study which found that patients treated with methadone were nearly four times more likely to die in periods off treatment [4]. Of note is the numbers of those ever treated for substance dependence (94.7%). Accessing treatment offers an opportunity to target overdose strategies to this at-risk group. Consideration should be given to expanding opioid overdose strategies to services providing treatment for all drug types. This strategy is further supported by the study's finding that the majority of fatal methadone-related overdoses were poly-substance in nature, as evidenced in the literature [4, 9, 12,13, 24]. Some of those who died where methadone was implicated may not be opioid dependant and the use of diverted methadone may be experimental or used for the purpose of self-medicating for example withdrawal symptoms from other drugs. While significant numbers of those who died had previous contact with drug treatment services, the data available did not indicate if these were OAT providers.

Retaining patients in OAT is an essential component of any national overdose prevention strategy [1, 6, 23]. This includes easy access, in a timely fashion, to OAT which should include the option of buprenorphine. OAT in Ireland [8] has expanded hugely over the past two decades with numbers in treatment expanding to over ten thousand. This accounts for approximately 50% of identified opioid users. Despite this high coverage there are still significant waiting times for OAT in some parts of the country with very limited access to buprenorphine as an alternative option to methadone. There is also concern that the OAT delivery models are preventing some opioid dependant patients, in particular those with over the counter (OTC) and prescribed opioid dependence accessing appropriate services [27]. Cousins et al. [4] reported that whilst numbers on methadone treatment are on the increase in Ireland, with a third treated in primary care, no corresponding decrease in deaths from opioid overdose has been recorded. This may, in part, be due to the above identified issues but also methadone diversion may be a contributing factor. The benefits and protection afforded by OAT may be eroded by methadone diversion [4,16]. Further research is needed to establish the extent to which diversion contributes to methadone-related deaths in Ireland. Supervision of methadone, known to reduce overdose, is intrinsic to OAT in Ireland [8]. National OAT guidelines recommend full supervision in the first three months during the induction and stabilisation phases and thereafter reduced with increasing stability. The guidelines also recommend at least one methadone dose to be supervised weekly with doses of 80mls or more supervised

at least twice weekly. Despite these guidelines, most methadone-related deaths in Ireland appear to be due to diverted methadone.

A third of methadone-related deaths are in patients accessing OAT. These patients are in contact with services, which provides a unique opportunity to risk assess and engage them in overdose prevention interventions such as overdose recognition, Cardio Pulmonary Resuscitation (CPR) and naloxone administration training. This study found that the majority of patients were not alone and were in a private dwelling at the time of the fatal overdose which supports the involvement of peers and family in overdose prevention programs. Of note was the low numbers of fatal overdoses occurring in homeless centres. Given that homelessness significantly increases mortality among opioid users and the high level of homelessness experienced by drug users in Ireland, this finding was contrary to what might be expected. It may be explained in part by the fact that OAT homeless accommodation in Ireland are staffed by experienced and well trained staff knowledgeable on the signs and treatment of overdose and the multi-occupancy of the sleeping accommodation where overdoses might be witnessed by third parties.

This national study is unique in an Irish context and is one of only a few studies that looks specifically at methadone-related deaths, and includes all patients dying over a two-year period in Ireland. Given the use of four different data sources by the NDRDI is it very unlikely that methadone-related deaths were missed or that duplications occurred. The missing data was due to it not being present in the original data sources used to populate the NDRDI. The number of different variables included in the data set are ambitious and if all data was available would provide a unique insight into this cohort. Consideration should be given to expanding data sources for the register, including the use of a standardised template that could be completed by the treatment provider at the time of death or last treatment provider known.

A number of limitations were identified in this study. Data was incomplete for many of the characteristics because it was not always available in the data sources that the NDRDI have access to. This makes analysis and interpretations difficult. The researchers, where possible, have identified the real denominator in the tables to clarify findings. The research is also limited by not being able to differentiate the different groups represented by those not registered for OAT. This includes: those never treated, just completed treatment, on waiting lists for OAT or in receipt of buprenorphine. There are also limitations in the interpretation of the "on CTL" group. These may include patients who have ceased OAT in the past 28 days but have not yet been exited from the register as patients remain on the treatment register for one month post treatment completion or default from treatment. This group is considered a high-risk group for overdose [4, 6,10, 20, 26] and has the potential to underestimate the numbers dying off treatment.

5. Conclusions

Methadone-related fatal overdose is a significant cause of death in young men in Ireland. This unique population share many of the same characteristics as other drug-related deaths [4, 11, 13, 18, 19, 22, 24, 25]. These are male gender, age (mid to late thirties), previous history of contact with treatment services, history of injecting drugs, high levels of mental illness, polysubstance toxicology on post-mortem and not in receipt of OAT. The majority dying from methadone-related overdose were not alone at the time of death and died in a private dwelling. The majority of patients were not on OAT at the time of the overdose but had previous contact with drug treatment services. These factors combined with other identified patient characteristics along with improved risk assessment and OAT retention strategies should inform any Irish national drug overdose plan. Improving access to more data sources for the NDRDI would provide more comprehensive data and further assist with targeting overdose prevention strategies.

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Conflict of interest

All authors declare no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

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