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Gender comparison in the history of addiction, specific psychopathology, behavioural covariates of heroin craving, and heroin post-traumatic stress disorder spectrum during agonist opioid treatment

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Summary

Introduction: Gender health is an interdisciplinary issue of medicine, raised by the need to account for sex-related influences on physiology and pathophysiology, that is, how symptoms, prevention strategies and treatment should vary by sexual gender. **Methods:** The basic purpose of this study is to estimate the magnitude of differences between females and males regarding the natural course of heroin addiction, the psychopathology specific to HUD, the behavioural covariates of heroin craving and the Heroin-Post Traumatic Stress Disorder Spectrum (H-PTSD/S) during an Agonist Opioid Treatment (AOT). **Results:** Our female patients tend to have a higher educational level and live in a family context more often than their male peers. They achieve the same level of adjustment as males during treatment and have a similar addiction history, with the same baseline grade of severity of addictive symptoms. Nevertheless, they are more depressed along the “Worthlessness/Being Trapped” (W/BT) dimension, have prominent panic anxiety more often than males, and, most conspicuously, they react differently to traumatic and loss events. They report perception of loss in relation to a higher number of events, and their reactions are more intense, with higher severity of post-traumatic stress disorder symptoms, such as flashbacks and avoidant behaviour. They are also more likely to display a H-PTSD/S clinical picture such as that reported for L’Aquila earthquake survivors. **Conclusion:** A female-tailored AOT treatment programme is already necessary and achievable in the approach to heroin addiction.

Key Words: History of addiction; psychopathology; heroin craving; heroin post-traumatic stress spectrum; agonist opioid treatment

1. Introduction

Gender health is an interdisciplinary issue of medicine, raised by the need to account for sex-related influences on physiology and pathophysiology, that is, how symptoms, prevention strategies, and treatment should vary by sexual gender. Third millennium medicine should not miss the chance to address such differences, as long as general models may be unsatisfactory for either sex, or pose major

limitations to effective prevention, retention in treatment and the achievement of good life quality. Gender health is not limited to the issue of gender-specific diseases, which will manifest exclusively in either sex (for instance, andrological and gynaecological illnesses), but should include gender-related factors from the very beginning of the approach to diseases afflicting both, such as cardiovascular diseases, cancer, metabolic disorders, infective disorders etc. [3].

In one of our studies we attempted to analyse

potential gender differences among a group of heroin addicts seeking treatment at our University-based Dual Disorder Unit. The central modality of treatment at our centre is the use of Methadone Maintenance. Among the patients who enter this programme there seems to be an emerging pattern of males who tend to use heroin as their opiate of choice, and are more likely to combine it with cannabis, while females are more likely to use 'street methadone', with the adjunctive use of ketamine, benzodiazepines, hypnotic drugs and/or amphetamines. Women are at higher risk of abusing opioids by following a pathway of initial prescription painkiller use, then resorting later to 'street methadone' to cope with prescription pain killer addiction. This latter pattern seems to result in running an increased risk of fatal accidental overdoses [45].

Proceeding along this line of research, our international research group studied intentional self-poisoning versus other methods of suicide in illicit substance users, according to gender [32, 33]. Illicit drug users show a high risk factor for fatal poisoning. In a cohort of Slovenian illicit drug users during the years 2002-2007, we differentiated between intentional and unintentional fatal poisoning, using demographic and toxicological data. 47.4% of our subjects committed fatal poisonings with undetermined intent, 26.5% with accidental intent and 26.1% with full intent. Age at suicide was lowest for accidental intoxications and highest for intentional intoxication. Half of the victims in cases of intentional intoxication were females. Widows/widowers were better represented in the intentional poisoning group. Alcohol intoxication was found less frequently in that same group; opioids were found less frequently in the intentional group; cocaine was found more frequently in accidental intoxications and only minimally in intentional intoxication. Regarding predictors of intentional intoxication, gender (males), age (older) and alcohol were the most discriminant characteristics. Out of 356 cases of Drug Related Drug (DRD), we described 106 (64 males and 42 females) DRD suicides. Of these, 65.1% were due to intentional self-poisoning by drugs, 28.3% were due to other methods for committing suicide, and 6.6% utilised intentional poisoning together with another method. Females were older than males; self-poisoning with benzodiazepines was more frequent in females and, in our study, no females were self-harmed by hanging, suffocation, or firearms. In females, age was tested as a risk factor that has proved to be more important than

suicide modality, but the use of benzodiazepines in female illicit drug users should be considered a critical issue with increasing age.

Aim: The main aim of this study has been to investigate gender-related differences in Heroin Use Disorder (HUD) patients in Agonist Opioid Treatment (AOT). More precisely, we focused on pre-treatment differences affecting addiction histories, psychopathological dimensions while on treatment, and stress reactivity in relation to loss and traumatic events.

2. Methods

2.1. Design of the study

This was a naturalistic, observational, cross-sectional study, with a single evaluation of a cohort of HUD patients during an AOT. The basic purpose of this kind of design is to estimate the magnitude of a phenomenon; in this case we estimated the magnitude of differences between females and males regarding the natural course of heroin addiction, the psychopathology specific to HUD, the behavioural covariates of heroin craving and the H-PTSD/S during an AOT. The research non-interventional protocol was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All the subjects examined signed an informed consensus form to qualify for participation in this study. Both the consent form and the experimental procedures were approved by the Ethics Committee of the University of Pisa, in accordance with internationally accepted criteria for ethical research.

2.2. Sample

The setting of the treatment featured the following characteristics: outpatient treatment; easy access to therapy; delivering of different types of interventions for addictive disorders and related problems (detoxification, methadone-, buprenorphine-, naltrexone-maintenance, general medical care, counselling, rehabilitative services, and psychological-psychiatric care) dosing of methadone soon after diagnosis of opioid dependence (with physical dependence); participation of patients in determining methadone dose and knowledge of the dose dispensed; urine specimens collected on a weekly basis and analysed for morphine and cocaine (availability of 1-3 results per

month).

Patients included in the study were selected on the basis of the following characteristics: over 17 years of age; admittance to methadone treatment not involving a detoxification plan (i.e. the progressive reduction of methadone dosages to zero); followed for at least one year of treatment.

The sample was made up of 98 patients, who were 20-59 years old (41 ± 9 years on average); 60 (61.2%) had a low level of education (with a duration of less than 8 years), 66 (67.3%) were without partners; 41 (41.8%) were unemployed; 25 (25.5%) had poor income and 12 (12.2%) were receiving disability benefits. 23 (23.5%) lived alone at the time of assessment. 77 (78.6%) patients were males, while 21 (21.4%) were females.

2.3. Assessment

2.3.1. Demographic data

To collect patients' demographic characteristics, we used a specific data collection card comprising: age, gender, education, marital status, employment, welfare benefits, householder employment, income, birth geographical area, birth location, geographical stay, residence location and living situation.

2.3.2. Drug Addiction History Questionnaire

Drug addiction history was recorded by using the Drug Addiction History Questionnaire (DAH-Q) [46]. DAH-Q is a multi-section questionnaire comprising the following sections: Physical health, mental health, social adjustment and environmental factors; anamnestic harmful substance use; clinical characteristics such as frequency of drug use, patterns of use, stages of illness; treatment history (current and past); addiction history (longitudinal characteristics). Items have been devised to elicit simple yes/no answers. The questionnaire allows us to make a judgment of impairment or not in 10 specific areas: impaired physical health and mental health, unsatisfactory employment, household, romantic involvement, socialization/leisure time, presence of legal problems, harmful polysubstance use, past treatments, and associated treatments.

2.3.3. Symptomatologic Check List (SCL90)

To record psychopathological symptoms, we used the Symptomatologic Check List (SCL90). Developed by Derogatis and colleagues [18], the SCL90 is made up of 90 items, each rated on a 5-point scale

of distress. It is a self-report clinical rating scale oriented towards the symptomatic behaviour of psychiatric outpatients. In the case of substance use disorders, the 90 items reflect five primary symptom dimensions: Worthlessness/Being trapped (W/BT), Somatic Symptoms (SS), Sensitivity/Psychoticism (S/P), Panic Anxiety (PA), and Violence/Suicidality (V/S) [48]. These five dimensions have been empirically established and primarily validated on a sample involving over 2,500 SUD patients [10, 11, 17, 37-41, 53-56, 59]. Based on the highest z scores obtained on the five SCL90 dimensions, subjects can be assigned to one of five mutually exclusive groups.

2.3.4. Inventory for assessing the behavioural covariates of craving (CRAV-HERO)

The presence and the severity of behavioural covariates of heroin craving were recorded by utilising Crav-Hero, an inventory for assessing the behavioural covariates of craving in HUD patients. Thirteen behaviours were selected. We clustered the 13 behaviours in 6 operating models. Exchange-related addictive behaviours (Exc-Behav) that aim to reveal the hierarchical approach applied by a subject to his/her values; (Time-related addictive behaviours (Time-Behav) that test the subject's ability to wait and manage the substance, and how much time is taken up thinking about the substance; Risk-related addictive behaviours (Risk-Behav) that are linked to the theme of risk in which the choice of whether to use a substance directly involves the patient's health and even life; Cue-induced/Environmental-related addictive behaviours (Cue/Env-Behav); Reward-craving induced behaviours (Rew-Behav); Relief-obsessive craving induced behaviours (Rel/Obs-Behav). Based on the highest z scores obtained on the five SCL90 dimensions, subjects can be assigned to one of five mutually exclusive groups. For details see [42].

2.3.5. Trauma and Loss Spectrum questionnaire (TALS)

The severity of emotional responses to life events was documented by the 'Trauma and Loss Spectrum' questionnaire (TALS). The TALS includes 116 items exploring the lifetime experience of a range of loss and/or traumatic events and lifetime symptoms, behaviours and personal characteristics that might be manifestations and/or risk factors for the development of a stress response syndrome [14]. For details and the use of this questionnaire in HUD patients, see [15]. Patients were divided into patients with and without heroin/PTSD spectrum (H/PTSD-S) using a

cut-off of 32. In the absence of life-threatening traumatic events and only because of their HUD disorder, H/PTSD-S patients have, over time, developed post-traumatic symptoms of the same severity as the young survivors of the L'Aquila earthquake who developed PTSD according to DSM criteria.

2.4. Data analysis

Males and females were subsequently compared for sociodemographic data, heroin addiction history, psychopathological symptoms and behavioural covariates of heroin craving. At the univariate level, the comparisons between the two study groups were performed using, for continuous variables, the analysis of the T-Test in the case of a metric and that of the Wilcoxon Z-test in the case of a parametric distribution. For the categorical variables, however, we used the Chi-Squared test corrected by Bonferroni's z-test in cases where there were more than 2 categories. At multivariate level, the continuous and the categorical variables that were found to be significant in differentiating between groups were used as predictors for a logistic regression analysis. All analyses were carried out using the statistical package of SPSS (version 25.0). Since this is an exploratory study, statistical tests were considered significant at the $p < 0.05$ level.

3. Results

Table 1 displays variable comparisons by gender in our patients. As regards demographic features, educational and living variables are the only ones to be different: the majority of women, unlike men, have an educational level reflecting an experience lasting at least 8 years. Female heroin addicts mostly live in parental or marital families. The data for women show no differentiation for age, marital status, working status, economic rank, or rate of welfare benefits as a source of income.

Regarding drug addiction history gender differences, our female patients showed an addiction history very similar to that of their male peers. In particular, they did not show more frequently impaired physical health, or impaired mental health; in addition, they did not show unsatisfactory employment, an unsatisfactory household situation, an unsatisfactory romantic involvement, or unsatisfactory socialization/leisure time. So too during treatment they did not show more legal problems, or anamnesticly harmful co-substance use. Treatment history showed

no significant differences regarding the presence of past or current combined treatments.

Nevertheless, in women substance use displayed a higher lifelong rate of benzodiazepine use. Heroin use features were similar, with a stereotype of long-lasting heroin use punctuated by intervals of self-detoxification and unsuccessful attempts to stay clean, so eventually reaching the revolving door phase, along with a variety of expected addiction-related psychosocial consequences. Chronological features such as age at onset of heroin use, age at onset of disease, addiction length and age at first treatment were comparable too. As regards the severity of craving-related behaviour during treatment, women displayed a mild condition, with no gender-related differences. Behaviours accounting for time and risk issues are those least represented. In detail, women are more likely to experience urgency and decide to trade for substances, showing greater responsiveness to cues suggesting substance use. On the other hand, they are less prone to craving-related risk behaviours. As a trend, women have fewer prominent addictive behaviours, but that difference does not reach the threshold of a clear statistical significance. On psychopathological grounds, women tend to be more impaired, but the only discriminant dimension is that of W/BT, which can be labelled as the depressive dimension of addiction. Two dimensions do come close to the threshold of significance – the withdrawal dimension (SS) and the violence-suicidal one (V/S). The psychopathological profile as assessed three months after substance discontinuation shows similarities between the genders, all dimensions being slightly higher in women except panic anxiety, with z-test significance after applying Bonferroni's correction. Gender differences also emerged in the perception of traumatic events and harm sustained in terms of post-traumatic symptoms. During heroin addiction treatment in AOT and during abstinence from substances, women experienced loss events, but not traumas, more often than men. Their emotional reactions were globally more intense, especially in terms of emotional, physical and cognitive symptoms, and flashbacks followed by avoidant behaviour. Moreover, a higher percentage of women than men show a full-blown PTSD picture which does not differ in severity from that displayed by survivors of a major earthquake.

Table 1. Significant differences in 98 HUD patients during AOT

	Males N=77	Females N=21		
Demographics	N (%)	N (%)	Chi	p
Education (≤ 8 years)	52 (67.5)	8 (38.1)	6.02	0.014
Living Situation (Alone)	22 (28.9)	1 (5.0)	4.98	0.026
Heroin Addiction History				
Life-time concomitant harmful use of benzodiazepines	35(46.1)	15(71.4)	4.24	0.039
Post-Traumatic Stress Disorder Spectrum				
11. Presence of H/PTSD-S (TALS score >32)	40 (51.9)	18 (85.7)	7.78	0.005
Psychopathological typology				
1-Worthlessness-Being Trapped	13(16.9)a	4(19.0)a		
2-Somatic Symptoms	11(14.3)a	4(19.0)a		
3-Sensitivity-Psychoticism	14(18.2)a	4(19.0)a		
4-Panic Anxiety	27(35.1)a	2(9.5)b		
5-Violence-Suicide	12(15.6)a	21(33.3)a	6.61	0.158
Psychopathology specific to HUD	M \pm sd	M \pm sd	T	p
1-Worthlessness-Being Trapped severity	46.67 \pm 9.4	52.40 \pm 10.1	-2.34	0.026
Post-Traumatic Stress Disorder Spectrum				
1-Loss Events	5.30 \pm 2.30	6.52 \pm 2.20	-2.08	0.043
4-Reactions to Losses or Upsetting Events	8.00 \pm 6.24	10.71 \pm 4.86	-2.11	0.041
5-Re-experiencing	4.14 \pm 3.40	6.24 \pm 2.70	-2.95	0.005
10-Total score	39.08 \pm 29.37	51.14 \pm 20.45	-2.16	0.036

4. Discussion

The present study sheds light on some gender-related differences in HUD patients during AOT. Our female patients tend to have a higher educational level and live in a family context more often than their male peers. They achieve the same level of adjustment as males during treatment and have a similar addiction history, if the baseline grade of severity of addictive symptoms is equivalent. Even so, in the W/BT dimension they experience deeper depression; while they are subject to prominent panic anxiety less often than males, the most important finding is that they react differently to traumatic and loss events. They report a perception of loss in relation to a higher number of events, and their reactions are more intense, with higher severity of PTSD symptoms, such as flashbacks and avoidant behaviour. They are also more likely to display a full-blown PTSD clinical picture such as that reported for earthquake survivors.

As regards sociodemographic profiles, women have a higher educational level; in particular, they are twice as likely to have a high school diploma, and up to four times as likely to have a university degree. De-

spite that, the proportion of women with a stable job is lower than that of men, so that they are more likely to be economically dependent on someone else: more precisely, on their partner six times as much and on welfare grants three times as much, compared with men. Women are more often widows, or have separated or divorced and then remarried, and mostly live with their partners or alone with their children: in detail, the “living alone with children” condition is 14 times more likely than in men. The most outstanding datum is the percentage of patients actually living with their children, which is just 6.2% for men (out of 24% who are fathers), and 11.4% for women (out of 35% who are mothers). Detachment from children may be a barrier to treatment access, as long as it is somehow consequential on the acknowledgment of the addictive condition by Social Authorities [63]. Our data are consistent with the previous literature only as regards educational level, while other documented differences tend to be levelled during treatment. It should be noted that our sample is mostly made up of those with a long history of addiction that comprises multiple treatments, which may mean that being treated, even if not continuously, has a positive

lifetime impact on the stabilization of an addiction-related lifestyle, even if in the absence of a satisfactory outcome [34].

There is a dearth of studies in the literature about gender differences in the course of addiction, but two major Italian studies provide results on the issue: the Vedette study, accounting for the scenario of the late 90's, and a more recent one (2005-2009) carried out in North-Eastern Italy [63]. Data indicate a younger age for women at first enrolment, especially for primary heroin users, so that it is much more unlikely for women to display primary abuse profiles other than primary heroin use. Females start using heroin more often because they decide to share their current partner's habit – a scenario that is never encountered at all for men as a starting mode. Women have a higher rate of addiction to their primary substance of abuse and are more likely to use drugs intravenously and intramuscularly, which may depend on women being initiated to drug use by already addicted, often expert partners. However, the reasons for seeking treatment should be taken into account when interpreting such rough data: in fact, men are more likely to be referred for mandatory treatment than are women. Age at first therapeutic attempt and latency in developing addiction (understood as time interval between first use and full-blown addiction) are consistent with the available literature, women being younger when first seeking treatment and developing addiction more quickly.

The crucial role of male partners in situations where women develop addiction is pinpointed by some authors as the reason why women display drug use behaviours that are not gender-specific, in terms of frequency of use, recurrent abstinence and the rate of polyabuse patterns, as well as choosing injection (on at least one occasion). As regards polyabuse patterns, though, women tend to be oriented towards anxiolytic sedatives or amphetamines, whereas men mostly use alcohol and cannabis [45].

Maybe due to a history of recurrent enrolment in treatment programmes for addiction that goes back over time, the profile of addicted females tends to converge with those most often found for men in the following terms: somatic impairment, mental health, work problems, family problems, affective discomfort, leisure time impairment, legal issues, lifetime polyabuse, treatment history. On the whole, the parameter of average addiction severity is similar for men and women. The general stereotype of heavy, long-lasting heroin use, with repeated attempts to detach followed by relapse fits both genders, as long as

the psychosocial background of individuals or samples is similar at the onset of drug use. Since benzodiazepine use does not seem to be normalized by repeated treatment cycles, it may mirror a gender-specific proneness to benzodiazepine use before as well as during treatment: the known relationship between dose adequacy and persisting benzodiazepine use [35, 36, 47, 49] can be assessed as twice as important for the stabilization of women patients compared with that for men [44].

As for addictive behaviours, data to be found in the literature rightly focus on a few differences that are at least partly related to craving. Mortality rates are generally higher for men (death arising from any cause), as in Vedette1 study [4, 19], which reports higher rates of AIDS-related deaths for men but higher overdose rates for women.

Females are not considered to be at higher risk of seroconversion for HIV, HCV and HBV. Reasons include the higher physiological risk for sexually transmitted disease, the low propensity for safe sex practices (especially with reference to having unprotected intercourse with their addicted partner), prostitution and needle exchange [6].

It is commonly believed that men's risk of being infected with HIV mainly derives from sexual transmission due to unprotected intercourse, so that men will be more concerned about the possible HIV-positive status of their sexual partner. For women, on the other hand, the lack of protection during sexual intercourse is mainly related to being pregnant, whereas the infective risk is underrated, for milder as well as for more severe diseases [61]. Indeed, the attitude of women towards risks undergone during addiction seems to include pregnancy-related events (e.g. a higher rate of miscarriage and of procured abortion), which may be brought on by the less predictable menstrual cycle (it usually becomes irregular during heroin use), and proneness to unprotected intercourse [52].

Women seem be less sensitive to infective risk due to needle exchange than male addicts [7, 9, 51, 60]. Women mostly exchange needles with their partner [26], the woman being the one who borrows rather than lends [6]. In contrast, men tend to exchange needles with friends [5, 13]. Reconsidering the results of qualitative studies on infective complications related to drug use by Rhodes et al. [57] and Avilés et al. [1], both studies have shown that this kind of risk is closely related to the unequal distribution of power of choice in intimate man-woman relationships.

Women, in fact, often comply with the decisions of a male partner, for instance when choosing whether to use condoms, or when arguing about the need to use clean syringes for an injection. One further factor peculiar to females is the perceived meaning of intimate relationships, as displayed socially: women tend to expect exclusive sharing with one another and reciprocity, which may be translated into unconditional acceptance of a partner's condition, including lack of precautions and barriers despite a partner's known HIV positivity [6].

Sex trading is also an important source of risk for women, who are prone to resorting to unsafe sex trading as a means of raising money, especially during the advanced stages of addiction, when they are broke or homeless [7]. Unprotected sex, beyond risk blindness due to addictive urges, is also a way to earn more, since some clients will offer more or accept higher fees for condom-less intercourse [12].

Generally speaking, strategies to raise money differ by gender. Men often resort to criminal acts to supply themselves with the substances they use, and are prone to using aggressiveness to obtain money in a criminal way (by resorting to robberies, burglaries and extorsions) [28], whereas women engage in crime less often, preferring to trade sex for money, which is not in itself illegal in several countries. Nevertheless, even where barely legal, prostitution is at risk of leading to a woman becoming victimized in one way or another, whether by violent clients, the authorities or through sheer exploitation.

Craving-related behaviours are quite mild during treatment, and do not differ by gender. Addictive behaviours are fewer in female addicts, which means that treatment levels tend to degrade a drug-related lifestyle, while causing a wider pre/post treatment gap for women, whose addictive history is particularly jeopardizing.

We had already noticed that the SCL90 five psychopathological dimensions were similar between genders at treatment entry and did not vary according to the length of addiction history. The sex ratio was 1:3.7 for the V/S dimension, 1:4.5 for W/BT, 1:5 for PA, 1:6.4 for SS, 1:7.1 for S/P [43, 48]. Comparing the different treatment contexts, we showed that the psychopathological impairment of patients admitted to residential treatment was lower than that of outpatient peers: that result was reversed in the female subpopulation, for whom a higher severity was displayed by residential treatment patients [56]. Duration of heroin use and age did not explain that discrepancy.

In greater detail, the W/BT dimension was higher in outpatients, and in residential females with respect to residential males. The same ratio was observed for the SS, PA and V/S dimensions. S/P was equally well represented in the two sexes, but the scores of residential females were higher than those of males, with no age- or duration of addiction-related effects. Studying differences through prominent psychopathology, we observed that prominently SS and V/S patients were more likely to be referred to AOT in an outpatient setting, which was thought to offer a better fit to patients with withdrawal symptoms, aggressiveness and suicidal risk. Conversely, residential treatment was chosen for female patients with severe psychopathological impairment, although the link between such profiles and the choice of treatment context was quite clear. Psychiatric comorbidity has a gender-related impact on patients' addictive history: in a sample of 1,195 patients, dual diagnosis was associated with older age, female sex, worse economic status and a longer duration of disease [53]. These differences are consistent with those observed in other samples of heroin addicts [2, 8, 30, 50, 58, 62].

As for depression, it is known that women have a higher rate of depressive disorders [31], so much so that self-injurious behaviour and attempted suicide are almost three times and six times more likely in women, respectively. Such differences are detected both before and after the onset of heroin use [63]. Our results identify a statistically significant difference only for the W/BT dimension, which is the depressive dimension of addiction, whereas the V/S dimension proves to be similar between the sexes: therefore, treatment is likely to be more effective on impulsive aspects than depressive ones.

The most prominent differences were found for emotional reactions to traumatic events and the perception of loss. Few studies have focused on gender-related differences in cases of PTSD [27, 29]. Fullerton et al. assessed PTSD symptoms in a sample of female who had survived road accidents, finding higher scores in the flashback and avoidance symptomatological domains, as well as numbing and hyperarousal. Consistently with those results, Kobayashi and Delahanty recently reported a higher frequency among women for such symptoms as nightmares and night-time flushing, or thoughts about one key event. Moreover, women score higher for PTSD symptoms in general. In this study, sleep latency proved to be positively related to PTSD symptoms for men, but negatively for women. In a sample of survivors of the

L'Aquila earthquake in Italy, the frequency of PTSD was higher among women, with a higher average score, and with a higher incidence of the three new symptoms accounted for in the latest edition of DSM (reckless and self-jeopardizing behaviour).

Our research group tried to approach psychiatric disorders from a dimensional viewpoint. Consistently with the conceptual basis for previously developed scales for the evaluation of mood, anxiety, eating disorders, psychosis and substance use, we validated a structured clinical interview form for post traumatic and loss-related symptoms, grouped together as a spectrum of diagnosis-related dimensions (trauma and loss spectrum – TALS). The items include different traumatic experiences and potential loss events which individuals may be exposed to throughout their lives, together with a series of potential reactions and persistent symptoms that may be rooted in trauma or loss. It also accounts for mild levels of intensity (sub-threshold in terms of categorial diagnosis) and personality traits which enhance the risk of developing such symptoms [14].

Women are more susceptible to loss events than to traumatic ones. Taken as a whole, the emotional reaction of female patients is far more severe than that of their male peers, especially for symptoms of avoidance and flashbacks. Studies by the V.P. Dole group at Pisa University point out that the onset of PTSD may occur even after years of heroin addiction, so that it was possible to inquire into a relationship between PTSD as a spectrum, and addiction-related variables, opiate medication dose and the duration of addiction history. In a sample of 82 patients in methadone treatment we found a close relationship between the PTSD spectrum score and the severity of heroin addiction. Moreover, we found an inverse correlation with methadone dose [16]. Lastly, in a comparative study, we compared earthquake survivors (with and without a history of subsequent PTSD) and heroin-addicted patients who had never experienced such traumatic events. We first performed a ROC preliminary analysis on total TALS scores stored on our database, in order to establish a cut-off to discriminate patients with a categorial (SCID) PTSD and non-PTSD diagnosis. Analysis found the 32 score level was the optimal intersection between the sensitivity and specificity of TALS' power to discriminate. Applying that cut-off to samples of heroin addicts, the percentage of subjects over the threshold was the same as in populations of PTSD earthquake survivors, and higher than that found among non-PTSD earthquake sur-

vivors. Further, all the TALS score domains failed to discriminate heroin-addicted patients from those who had developed PTSD after an earthquake, while both those groups differed from the non-PTSD subgroup. These results indicate a close resemblance between heroin-addicted patients and PTSD earthquake survivors as to emotional reaction to loss and traumatic events, and confirm the potential role of opioid mediators in the physiopathology and pathogenesis of PTSD [15].

If it is true that years of heroin addiction may favour the onset of PTSD, women seem to be particularly vulnerable to it. In our study, 85% of women (vs. 52% of men) show a level of PTSD spectrum symptoms comparable with that of earthquake survivors with a categorically assigned PTSD diagnosis. Lastly, given that higher methadone dosages show a direct correlation with a lower level of PTSD symptoms, PTSD can be seen as a new criterion for the use of higher dosages in female patients, together with the late stage of pregnancy [20-25, 64-66].

5. Conclusions

Gender-related differences can be found both for the natural history of heroin addiction and once therapy has begun. Women on treatment tend to have a higher educational level than men and are more likely to live within families. The two gender profiles are similar during therapy with respect to social adjustment in cases where the addictive backgrounds are equivalent. No differences emerge for addictive behaviour, while the psychopathological profiles of female patients are characterized by a higher of depression along the W/BT dimension and a lower prominence of panic anxiety. The most important difference concerns post-traumatic adjustment; in that phase women show a higher level of PTSD spectrum severity and, categorically, a PTSD diagnosis, together with a higher number of perceived loss events. OAT seems to have a positive impact on all PTSD spectrum dimensions. A female-tailored treatment programme is already necessary and achievable in the approach to be taken in treating heroin addiction.

References

1. Avilés N. R., Barnard M., Rhodes T., Hariga F., Weber U., Coppel A., Fountain J. (2000): Qualitative research on the health risks associated with drug injecting: needle and syringe sharing. In: Fountain J. (Ed.) *Understanding and responding to drug use: the role of qualitative*

- research. EMCCDDA Scientific Monograph. Available at www.emccdda.eu.
2. Back S. E., Payne R. L., Wahlquist A. H., Carter R. E., Stroud Z., Haynes L., Hillhouse M., Brady K. T., Ling W. (2011): Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. *Am J Drug Alcohol Abuse*. 37(5): 313-323.
 3. Baggio G., Corsini A., Floreani A., Giannini S., Zagonel V. (2013): Gender medicine: a task for the third millennium. *Clin Chem Lab Med*. 51(4): 713-727.
 4. Bargagli A. M., Davoli M., Minozzi S., Vecchi S., Perucci C. A. (2007): A Systematic Review of Observational Studies on Treatment of Opioid Dependence. . Accessed 1/2/2019, Available at <http://www.who.int>
 5. Barnard M. A. (1993): Needle sharing in context: patterns of sharing among men and women injectors and HIV risks. *Addiction*. 88(6): 805-812.
 6. Brener L., Treloar C. (2008): Injecting practice between sexual partners. A summary of the literature, National Centre in HIV Social Research. Accessed 10/5/2019, Available at <http://nchr.arts.unsw.edu.au>
 7. Burroni P., Vigna-Taglianti F. D., Versino E., Beccaria F., Garnieri M., Mathis F., Picciolini A., Rotelli M., Bargagli A. M. (2007): Gender Differences in Heroin Addiction and Treatment. Monograph N° 7. Vedette group, Torino.
 8. Cacciola S. J., Alterman A. I., Rutherford M. J., McKay J. R., Mulvaney F. D. (2001): The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend*. 61: 271-280.
 9. Callaghan R. C., Cunningham J. A. (2002): Gender differences in detoxification: predictors of completion and re-admission. *J Subst Abuse Treat*. 23(4): 399-407.
 10. Carbone M. G., Maiello M., Spera V., Manni C., Pallucchini A., Maremmani A. G. I., Maremmani I. (2018): The SCL90-based psychopathological structure may be applied in Substance Use Disorder patients independently of the drug involved, even in heroin, alcohol and cocaine monodrug users. *Heroin Addict Relat Clin Probl*. 20(5): 29-34.
 11. Carbone M. G., Tagliarini C., Ricci M., Lupi A. M., Sarandrea L., Ceban A., Casella P., Maremmani I. (2019): Ethnicity and specific psychopathology of addiction. Comparison between migrant and Italian Heroin Use Disorder patients. *Heroin Addict Relat Clin Probl*. 21(5): 61-66
 12. Cusick L. (2006): Widening the harm reduction agenda: From drug use to sex work. *Int J Drug Policy*. 17(1): 3-11.
 13. Davies A. G., Dominy N. J., Peters A. D., Richardson A. M. (1996): Gender differences in HIV risk behaviour of injecting drug users in Edinburgh. *AIDS Care*. 8(5): 517-527.
 14. Dell'Osso L., Carmassi C., Rucci P., Conversano C., Shear M. K., Calugi S., Maser J. D., Endicott J., Fagiolini A., Cassano G. B. (2009): A multidimensional spectrum approach to post-traumatic stress disorder: comparison between the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS) and the Self-Report instrument (TALS-SR). *Compr Psychiatry*. 50(5): 485-490.
 15. Dell'Osso L., Massimetti E., Rugani F., Carmassi C., Fared A., Stratta P., Rossi A., Massimetti G., Maremmani I. (2015): Life events (loss and traumatic) and emotional responses to them in acute catastrophe survivors and long-lasting heroin use disorder patients never exposed to catastrophic events. *Heroin Addict Relat Clin Probl*. 17(6): 49-58.
 16. Dell'Osso L., Rugani F., Maremmani A. G., Bertoni S., Pani P. P., Maremmani I. (2014): Towards a unitary perspective between post-traumatic stress disorder and substance use disorder. Heroin use disorder as case study. *Compr Psychiatry*. 55(5): 1244-1251.
 17. Della Rocca F., Maremmani A., Rovai L., Bacciardi S., Lamanna F., Maremmani I. (2017): Further evidence of a specific psychopathology of Heroin Use Disorder. Relationships between psychopathological dimensions and addictive behaviors. *Heroin Addict Relat Clin Probl*. 19(6): 13-20.
 18. Derogatis L. R., Lipman R. S., Rickels K. (1974): The Hopkins Symptom Checklist (HSCL). A self report symptom inventory. *Behav Sci*. 19: 1-16.
 19. Emccdda (2006): A gender perspective on drug use and responding to drug problems. . Accessed 1/1/2019, Available at www.emccdda.europa.eu
 20. Finnegan L., Amass L., Jones H., Kaltenbach K. (2004): Addiction and Pregnancy. *Heroin Addict Relat Clin Probl*. 7(4): 5-22.
 21. Finnegan L., Pacini M., Maremmani I. (2009): Clinical Foundation for the Use of Methadone During Pregnancy and Breast-feeding. In: Maremmani I. (Ed.) *The Principles and Practice of Methadone Treatment*. Pacini Editore Medicina, Pisa. pp. 189-196.
 22. Finnegan L., Pacini M., Maremmani I. (2010): Methadone treatment for pregnant heroin addicted women. *Heroin Addict Relat Clin Probl*. 12(2): 29-36.
 23. Finnegan L. P. (1995): Addiction and Pregnancy: Maternal and Child Issues. In: Tagliamonte A., Maremmani I. (Eds.): *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien New York. pp. 137-147.
 24. Finnegan L. P. (2000): Women, pregnancy and methadone. *Heroin Addict Relat Clin Probl*. 2(1): 1-8.
 25. Finnegan L. P., Kandall S. R. (1997): Maternal and neonatal effects of alcohol and drugs. In: Lowinson J. H., Ruiz P., Millman R. B. (Eds.): *Substance Abuse: A Comprehensive Textbook 2nd ed*. Williams & Wilkins, Baltimore, Md. pp. 513-564.
 26. Freeman R. C., Rodriguez G. M., French J. F. (1994): A comparison of male and female intravenous drug users' risk behaviors for HIV infection. *Am J Drug Alcohol*

- Abuse*. 20(2): 129-157.
27. Fullerton C. S., Ursano R. J., Epstein R. S., Crowley B., Vance K., Kao T. C., Dougall A., Baum A. (2001): Gender differences in posttraumatic stress disorder after motor vehicle accidents. *Am J Psychiatry*. 158(9): 1486-1491.
 28. Kauffman S. E., Silver P., Poulin J. (1997): Gender differences in attitudes toward alcohol, tobacco, and other drugs. *Social Work*. 42(3): 231-241.
 29. Kobayashi I., Delahanty D. L. (2013): Gender differences in subjective sleep after trauma and the development of posttraumatic stress disorder symptoms: a pilot study. *J Trauma Stress*. 26(4): 467-474.
 30. Kosten T. R., Rounsaville B. J., Kleber H. D. (1985): Ethnic and gender differences among opiate addicts. *Int J Addict*. 20(8): 1143-1162.
 31. Kuehner C. (2003): Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. *Acta Psychiatr Scand*. 108(3): 163-174.
 32. Lovrecic M., Lovrecic B., Selb Semerl J., Maremmani I. (2015): Suicide by narcotic poisoning in Slovenia, according to gender, during the period 2004-2007. *Heroin Addict Relat Clin Probl*. 17(4): 77-84.
 33. Lovrecic M., Lovrecic B., Šemerl J. Š., Maremmani A. G. I., Maremmani I. (2013): Intentional self-poisoning versus other methods of suicide in illicit drug users, according to gender. *Heroin Addict Relat Clin Probl*. 15(2): 57-62.
 34. Lovrecic M., Lovrecic B., Semerl J. S., Maremmani I., Maremmani A. G. I. (2016): The filing of addicts at addiction units is correlated with a reduction in mortality due to illicit opioids, but also to prescribed opioids and other substances of abuse. *Heroin Addict Relat Clin Probl*. 18(3): 15-22.
 35. Maremmani A. G. I., Bacciardi S., Rugani F., Rovai L., Massimetti E., Gazzarrini D., Dell'osso L., Pani P. P., Pacini M., Maremmani I. (2014): Outcomes of clonazepam maintained benzodiazepine-heroin addicted patients during methadone maintenance: A descriptive case series. *Heroin Addict Relat Clin Probl*. 16(3): 55-64.
 36. Maremmani A. G. I., Bacciardi S., Rugani F., Rovai L., Massimetti E., Gazzarrini D., Dell'Osso L., Pani P. P., Pacini M., Maremmani I. (2014): Is it possible to treat heroin addicts with severe comorbid benzodiazepines addiction combining enhanced methadone maintenance and clonazepam maintenance treatments? *Heroin Addict Relat Clin Probl*. 16(4): 15-24.
 37. Maremmani A. G. I., Cerniglia L., Cimino S., Bacciardi S., Rovai L., Rugani F., Massimetti E., Gazzarrini D., Pallucchini A., Pani P. P., Akiskal H. H., Maremmani I. (2015): Towards a specific psychopathology of heroin addiction. Comparison between Heroin Use Disorder and Major Depression patients. *Heroin Addict Relat Clin Probl*. 17(6): 9-16.
 38. Maremmani A. G. I., Gazzarrini D., Fiorin A., Cingano V., Bellio G., Perugi G., Maremmani I. (2018): Psychopathology of addiction: Is the SCL90-based five dimensional structure applicable to a non-substance-related addictive disorder such as Gambling Disorder? *Ann Gen Psychiatry*. 17(3): 1-9.
 39. Maremmani A. G. I., Lovrecic M., Lovrecic B., Maremmani I. (2019): Ethnicity and specific psychopathology of addiction. Comparison between Slovenian and Italian Heroin Use Disorder patients. *Heroin Addict Relat Clin Probl*. 21(4): 35-39.
 40. Maremmani A. G. I., Maiello M., Carbone M. G., Pallucchini A., Brizi F., Belcari I., Conversano C., Perugi G., Maremmani I. (2018): Towards a psychopathology specific to Substance Use Disorder: Should emotional responses to life events be included? *Compr Psychiat*. 80: 132-139.
 41. Maremmani A. G. I., Pani P. P., Rovai L., Bacciardi S., Maremmani I. (2017): Towards the identification of a specific psychopathology of Substance Use Disorders. *Front Psychiatry*. 8(68).
 42. Maremmani A. G. I., Rovai L., Bacciardi S., Massimetti E., Gazzarrini D., Rugani F., Pallucchini A., Piz L., Maremmani I. (2015): An inventory for assessing the behavioural covariates of craving in heroin substance use disorder. Development, theoretical description, reliability, exploratory factor analysis and preliminary construct validity. *Heroin Addict Relat Clin Probl*. 17(5): 51-60.
 43. Maremmani A. G. I., Rovai L., Maremmani I. (2012): Heroin addicts' psychopathological subtypes. Correlations with the natural history of illness. *Heroin Addict Relat Clin Probl*. 14(1): 11-22.
 44. Maremmani I., Balestri C., Sbrana A., Tagliamonte A. (2003): Substance (ab)use during methadone and naltrexone treatment. Interest of adequate methadone dosage. *J Mainten Addict* 2(1-2): 19-36.
 45. Maremmani I., Canoniero S., Pacini M., Maremmani A. G. I., Carlini M., Golia F., Deltito J., Dell'osso L. (2010): Differential Substance Abuse Patterns Distribute According to Gender in Heroin Addicts. *J Psychoactive Drugs*. 42(1): 89-95.
 46. Maremmani I., Castrogiovanni P. (1989): Drug Addiction History Questionnaire (DAH-Q) - Heroin Version. University Press, Pisa.
 47. Maremmani I., Pani P. P., Mellini A., Pacini M., Marini G., Lovrecic M., Perugi G., Shinderman M. (2007): Alcohol and cocaine use and abuse among opioid addicts engaged in a methadone maintenance treatment program. *J Addict Dis*. 26(1): 61-70.
 48. Maremmani I., Pani P. P., Pacini M., Bizzarri J. V., Trogu E., Maremmani A. G. I., Perugi G., Gerra G., Dell'osso L. (2010): Subtyping Patients with Heroin Addiction at Treatment Entry: Factors Derived from the SCL-90. *Ann Gen Psychiatry*. 9(1): 15.
 49. Maremmani I., Shinderman M. S. (1999): Alcohol, benzodiazepines and other drugs use in heroin addicts treated with methadone. Polyabuse or undermedication?

- Heroin Addict Relat Clin Probl.* 1(2): 7-13.
50. Mazza M., Mandelli L., Di Nicola M., Harnic D., Catalano V., Tedeschi D., Martinotti G., Colombo R., Bria P., Serretti A., Janiri L. (2009): Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. *J Affect Disord.* 115(1-2): 27-35.
 51. Montgomery S. B., Hyde J., De Rosa C. J., Rohrbach L. A., Ennett S., Harvey S. M., Clatts M., Iverson E., Kipke M. D. (2002): Gender differences in HIV risk behaviors among young injectors and their social network members. *Am J Drug Alcohol Abuse.* 28(3): 453-475.
 52. Nelson Z. L., Kauffman M. D., Morrisone D. M. (1995): Gender differences in drug addiction treatment: implication for social work intervention with substance abusing women. *Social Work.* 40(1): 45-54.
 53. Pani P.P., Maremmani A. G. I., Trogu E., Vigna-Taglianti F., Mathis F., Diecidue R., Kirchmayer U., Amato L., Davoli M., Ghibaudi J., Camposeragna A., Saponaro A., Faggiano F., Maremmani I. (2016): Psychic Structure of Opioid Addiction: Impact of Lifetime Psychiatric Problems on SCL-90-based Psychopathologic Dimensions in Heroin-dependent Patients. *Addict Disord Their Treatment.* 15(1): 6-16.
 54. Pani P.P., Maremmani A. G. I., Trogu E., Vigna-Taglianti F., Mathis F., Diecidue R., Kirchmayer U., Amato L., Davoli M., Ghibaudi J., Camposeragna A., Saponaro A., Faggiano F., Maremmani I. (2015): Psychopathological symptoms in detoxified and non-detoxified heroin-dependent patients entering residential treatment. *Heroin Addict Relat Clin Probl.* 17(2-3): 17-24.
 55. Pani P.P., Maremmani A. G. I., Trogu E., Vigna-Taglianti F., Mathis F., Diecidue R., Kirchmayer U., Amato L., Ghibaudi J., Camposeragna A., Saponaro A., Davoli M., Faggiano F., Maremmani I. (2016): Psychopathology of addiction: May a SCL-90 based five dimensions structure be applied irrespectively of the involved drug? *Ann Gen Psychiatry.* 15:13.
 56. Pani P. P., Trogu E., Vigna-Taglianti F., Mathis F., Diecidue R., Kirchmayer U., Amato L., Davoli M., Ghibaudi J., Camposeragna A., Saponaro A., Faggiano F., Maremmani A. G., Maremmani I. (2014): Psychopathological symptoms of patients with heroin addiction entering opioid agonist or therapeutic community treatment. *Ann Gen Psychiatry.* 13(1): 35.
 57. Rhodes T., Barnard M. A., Fountain J., Hariga F., Avilés N. R., Vicente J., Weber U. (2001): Injecting drug use, risk behaviour and qualitative research in the time of AIDS, EMCDDA Insight n. 4. Accessed 22/1/2019, Available at <http://www.emcdda.org>
 58. Ross J., Teesson M., Darke S., Lynskey M., Ali R., Ritter A., Cooke R. (2005): The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). *Drug Alcohol Rev.* 24(5): 411-418.
 59. Rugani F., Paganin W., Maremmani A. G. I., Perugi G., Maremmani I. (2019): Towards a specific psychopathology of heroin addiction. Comparison between Heroin Use Disorder and Chronic Psychotic patients. *Heroin Addict Relat Clin Probl.* 21(3): 53-59.
 60. Sherman S. G., Latkin C. A., Gielen A. C. (2001): Social factors related to syringe sharing among injecting partners: a focus on gender. *Subst Use Misuse.* 36(14): 2113-2136.
 61. Stocco P., Llopis Llacer J. J., Defazio L., Calafat A., Mendes F. (2000): Women drug abuse in Europe: gender identity. Accessed 3/2/2019, Available at https://www.drugsandalcohol.ie/3592/1/IREFREA_Women_drug_abuse_in_Europe.pdf.
 62. Teesson M., Havard A., Fairbairn S., Ross J., Lynskey M., Darke S. (2005): Depression among entrants to treatment for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence, correlates and treatment seeking. *Drug Alcohol Depend.* 78(3): 309-315.
 63. Vigna-Taglianti F. D., Burrioni P., Mathis F., Versino E., Beccaria F., Rotelli M., Garneri M., Picciolini A., Bargagli A. M., Vedette Study Group (2016): Gender Differences in Heroin Addiction and Treatment: Results from the VEdeTTE Cohort. *Substance Use & Misuse.* DOI: 10.3109/10826084.2015.1108339
 64. Zolesi O., Maremmani I. (1996): Principi clinici per l'utilizzo del metadone nella tossicodipendente da eroina in gravidanza. In: Maremmani I., Guelfi G. P. (Eds.): *Metadone Le ragioni per l'uso.* Pacini Editore, Pisa. pp. 55-60.
 65. Zolesi O., Maremmani I. (1998): Principi clinici per l'utilizzo del metadone nella tossicodipendente da eroina durante la gravidanza. *Medicina delle Tossicodipendenze - Italian Journal on Addictions.* VI(2): 39-44.
 66. Zolesi O., Maremmani I. (2001): Clinica e terapia dell'eroinomane in gravidanza. In: Maremmani I., Canoniero S., Pacini M. (Eds.): *Manuale di Neuropsicofarmacoterapia Psichiatrica e dell'Abuso di Sostanze.* Pacini Editore Medicina & AUC-CNS onlus, Pisa. pp. 427-435.

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All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest

Authors declared no conflict of interest. IM served as Board Member for Angelini, Camurus, CT Sanremo, D&A Pharma, Gilead, Indivior, Lundbeck, Molteni, MSD, Mundipharma

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.

Note

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