

Harm reduction program use, psychopathology and medical severity in patients with methadone maintenance treatment

Uso de reducción de daños y gravedad psicopatológica y médica en pacientes en programa de mantenimiento con metadona

NIEVES MARTÍNEZ-LUNA*,**,***; LAIA RODRIGUEZ-CINTAS****; ABDERRAMAN ESOJO*,**, RAÚL FELIPE PALMA-ÁLVAREZ*,**, MARÍA ROBLES-MARTÍNEZ*, **, LARA GRAU-LÓPEZ*, **,***; MARTA PEREA*,**, CARLOS RONCERO*,**,***,****

*Sección de Adicciones y Patología Dual. Servicio de Psiquiatría Hospital Universitario Vall d'Hebrón. ASPB, Barcelona (España).

**Servicio de Psiquiatría. Hospital Universitario Vall d'Hebrón. Barcelona. CIBERSAM (España).

***Departamento de Psiquiatría. Universidad Autónoma de Barcelona (España).

**** Psychiatric Service. University of Salamanca Health Care Complex (Complejo Asistencial Universitario de Salamanca/CAUSA), Salamanca, Spain. Institute of Biomedicine of Salamanca (IBSAL). University of Salamanca (Spain).

Abstract

Methadone maintenance programs (MMP) for opioid dependence treatment have been widely used due to their effective therapeutic outcomes. Harm reduction programs (HRP) are complementary programs for severe patients with high risk behaviors and when abstinence is not possible. This study aims to compare patients in MMP that use HRP (MMP-HRP) and patients in MMP who do not use HRP (MMP-NO HRP). The sample was composed of 143 patients (MMP-HRP = 42 vs. MMP-NO HRP = 101). An additional subanalysis was performed with patients under 45 years of age (n = 116; MMP-HRP = 38 vs. MMP-NO HRP = 78). All patients were assessed with an ad hoc socio-demographic questionnaire, EuropASI, SCID-I, and SCID-II. Results show that MMP-HRP patients were younger with more frequent use of intravenous drugs and with a high prevalence of Cluster B personality disorders. MMP-NO HRP patients had lower methadone doses compared to MMP-HRP patients and preferred to use drugs by smoked route more frequently. In the subanalysis of patients under 45, MMP-HRP patients were younger, had a higher prevalence of liver diseases, more intravenous drug use, greater severity on the drug use scale, less social and family support in the subscales of EUROP-ASI than compared to patients under 45 years in the group MMP-NO HRP. In conclusion, MMP-HRP patients are younger compared to MMP-NO HRP patients, they also receive higher doses of methadone and had more intravenous use. The above findings imply that the early onset of high risk drug use and long-term exposure to heroin have more severe outcomes such as higher comorbidities (e.g. infectious diseases, medical and psychiatric disorders), and consequently, these patients are a more vulnerable group with a worse prognosis.

Keywords: harm reduction program; methadone maintenance treatment; HIV, hepatitis C, heroine dependence.

Resumen

Los programas de mantenimiento con metadona (PMM) para el tratamiento de la dependencia a opiáceos han demostrado elevada eficacia, siendo los más utilizados en la actualidad. La Reducción de Daños (REDAN) se refiere a tratamientos y abordajes complementarios en personas con graves dificultades para la abstinencia y conductas de riesgo. El objetivo del presente trabajo es comparar pacientes en PMM que utilizan servicios REDAN (PMM-REDAN) versus pacientes en PMM que no utilizan servicios REDAN (PMM-NO REDAN). Se incluyó un total de 143 pacientes en PMM (PMM-REDAN = 42, PMM-NO REDAN = 101) y se realizó un subanálisis de los menores de 45 años (n = 116; 38 PMM-REDAN, 78 PMM-NO REDAN). Se hizo una evaluación de datos socio-demográficos, EuropASI, SCID-I y SCID-II. Los pacientes PMM-REDAN son más jóvenes, utilizan la vía parenteral y presentan trastornos de personalidad Clúster B comórbidos a la adicción. Los PMM-NO REDAN consumen más por vía fumada y tienen dosis bajas de metadona. Los menores de 45 años PMM-REDAN son más jóvenes, tienen mayor prevalencia de enfermedades hepáticas, utilizan más la vía parenteral, tienen un consumo de drogas más grave y menos soporte socio-familiar en las subescalas EUROP-ASI que los menores de 45 años PMM-NO REDAN. En conclusión, los pacientes PMM-REDAN son más jóvenes, reciben dosis mayores de metadona y utilizan vías de mayor riesgo, hecho que implica un inicio temprano en prácticas de consumo de riesgo, mayor tiempo de exposición a la heroína, con consecuencias de mayor gravedad de la adicción, mayor comorbilidad infecciosa, médica y psiquiátrica, siendo un grupo vulnerable y con pronóstico desfavorable.

Palabras clave: programa de reducción de daño; tratamiento de mantenimiento con metadona; VIH; hepatitis C; dependencia heroína.

Received: October 2016; Accepted: July 2017.

Send correspondence to:

Dra. Nieves Martínez-Luna. Sección de Adicciones y Patología Dual. Servicio de Psiquiatría. Hospital Universitario Vall d'Hebrón. Passeig Vall d'Hebrón 119-129. 08035 Barcelona. Phone +34 934893880. Fax +34 934894587. E-mail: ngmartin@vhebron.net.

The number of heroin users in Methadone Maintenance Programs (MMP) in Spain is estimated to be around 65,648 (Observatorio Español de la Droga y las Toxicomanías [Spanish Monitoring Centre for Drugs and Drug Addiction] [OEDT, 2015]). Heroin dependence is a chronic problem with a history of relapse. It is a problem associated with medical and mental disorders, and is exacerbated if associated with intravenous heroin use (Roncero et al., 2016; Miguel-Arias, Pereiro, Bermejo, López de Abajo & Sobrino, 2016).

Substitution programs with opioid agonists have demonstrated a high degree of efficacy and are currently the most widely used with patients with opioid dependence, as well as for reducing the prevalence of HIV infection (Amato, Davoli, Perucci, Ferri, Faggiano & Mattick, 2005; Fernandez-Miranda, García-Portilla, Sáiz, Gutiérrez & Bobes, 2001; MacArthur et al., 2014). Observational studies demonstrate its usefulness in terms of treatment retention capacity in MMP, reduction of illicit drug use, high-risk practices, comorbidity and morbi-mortality (HIV, viral hepatitis) and associated crime, as well in as improvements regarding the employment and quality of life of addicts (Fernández-Miranda et al., 2001; Havinga, van der Velden, de Gee & van der Poel, 2014; Salamina et al., 2010).

The response to methadone varies greatly (Marie-Claire et al., 2016), and some patients may require only low doses. However, methadone doses above 60-80 mg/day and easy access to care and psychosocial services are linked to greater treatment adherence and decreased drug use, although psychiatric comorbidity and substance dependence overshadow the prognosis (Amato et al., 2005; Fernández-Miranda et al., 2001).

It has been reported that among heroin addicts in opioid substitution treatment, 83% of patients present at least one clinical comorbidity, with 69% presenting some physical comorbidity and 59% and 40% with infectious and non-infectious comorbidity, respectively (Roncero et al., 2011). There is also a high prevalence of mental illness in opioid users (Fernández-Miranda et al., 2001; Herrero, Domingo-Salvany, Brugal, Torrens & Itinere Investigators, 2011; Roncero et al., 2016; San et al., 2016) with comorbidity in Axis I (52%) and Axis II (19%) (Roncero, et al., 2011). The most common mental disorder is mood disorder and the spectrum of anxiety disorders, with a lifetime prevalence of between 4% and 54%; The prevalence of other major psychiatric disorders such as schizophrenia, obsessive-compulsive disorder and eating disorders is lower (Astals, Díaz, Domingo-Salvany, Martín-Santos, Bulbena & Torrens, 2009).

Programs associated with treatment intervention in chronic drug users, in which heroin addicts have a significant percentage, are harm reduction programs (HRPs) (International Harm Reduction Association [IHRA], 2009). HR refers to policies, programs and

practices that seek to reduce the health, social and economic consequences associated with the use of psychoactive drugs among people who cannot or do not want to stop consumption (Daigre et al., 2010; IHRA, 2009). The main focus is on the prevention of harm for people who continue to use drugs, so these programs are included within tertiary prevention (Rhodes & Hedrich, 2010; Torrens, Fonseca, Castillo & Domingo-Salvany, 2013). Its objectives are to minimize the medical and psychopathological complications caused by drug use, to promote less invasive or dangerous methods of use, to teach healthy hygiene-dietary habits, to bring the patient progressively closer to healthcare resources and finally to encourage abstinence (IHRA, 2009). A particularly vulnerable group is young people, where a steady increase in rates of illicit drug use and related deaths from overdose, especially among those injecting the drugs, has been noted. Studies have shown that being young, frequently arrested, and with moderate/heavy alcohol use alongside recent hospitalization for methadone detoxification increases the risk of overdose (Seal, Kral, Gee, Moore, Bluthenthal, Lorvick, & Edlin, 2001).

HRPs provide partial and/or palliative measures for heavy users or those at risk of social exclusion. They seek to prevent the most prevalent infections (syringe exchange programs and distribution of condoms) and increase the control and treatment of organic and psychiatric disease associated with drug use (easy access close to health services). In Spain, methadone treatment programs at the public level began in 1985, although they did not expand until the 1990s with therapeutic and HR approaches. Syringe exchange programs (SEPs) were also started around the same time, with facilities for selfinjection use or supervised consumption included in 2000 (Martínez-Luna, Palma-Álvarez & Roncero, 2016).

The aims of the study are to compare patients in MMPs who use MMP-HRP services to patients in MMP-NO HRP. It is hypothesized that MMT-HR patients have greater addiction severity and greater comorbidity in both physical (HIV, Hepatitis C) and mental diseases, with more clinical-psychopathological complexity than MMP-NO HRP.

Method

The study was carried out at the Vall d'Hebron Outpatient Drug Clinic (CAS). The data were collected from January 2006 to January 2016. Inclusion criteria were: to be over 18 years, present opioid dependence according to DSM IV-TR and DSM-5 criteria, sign informed consent and to complete the assessment process, the protocol of which had previously been approved by the Hospital Ethics Committee. Exclusion criteria were: to show signs of intoxication, severe somatic illness, severe cognitive impairment and language barrier, all of which were

checked in the baseline interview. Patients received no financial compensation for their participation in the study. This paper is part of wider research on comorbidity in patients with substance dependence disorders.

Of the 225 patients who met the diagnostic criteria for opioid dependence disorder or moderate/severe drug use disorder according to DSM-IV-TR criteria (2006-2013) and DSM-5 (2014-2016) and were in MMP, 143 patients completed the psychological assessment protocol. The sample was divided into two groups: the first consisted of patients in PMM-NO HRP (n=101) and the second was composed of patients in MMP-HRP (n=42). To be included in the latter group patients needed to have used 2 or more harm reduction services (syringe exchange, supervised drug consumption room, overdose workshop).

We also performed a subanalysis of those under the age of 45 in the final group of 143 patients. This subanalysis was based on an approximate calculation of the generation of users to whom HRP services began to be offered in a generalized manner in Spain. The sample was divided between the generation previous to HRP (older than 45) and the generation after the start of HRP (under 45), which left a sample of 116 patients, with 78 patients in the MMP-NO HRP group and 38 in the MMP-HRP group.

Variables and Instruments

Three diagnostic interviews were performed by trained psychologists to collect sociodemographic data (sex, age, nationality, level of education), variables related to

opioid use (age of dependence onset, quantity consumed, methadone dosage). The instruments used were:

- A sociodemographic and clinical questionnaire developed ad hoc by our unit that includes infectious diseases (HIV, tuberculosis, etc.) and hepatic diseases (hepatopathies, cirrhosis, infectious hepatitis or other hepatitis) (Grau-López et al., 2012).
- The Spanish version (Bobes, González, Saiz & Bousoño, 1996) of EuropASI, the European adaptation of the Addiction Severity Index (Kokkevi & Hartgers, 1995). This structured and heterogeneous clinical interview explores the following areas: medical problems, employment status/support, alcohol/drug use, legal problems, social and family relationships and psychological state. Composite scores have been used to control the interviewer's degree of subjectivity.
- SCID-I (Semi-structured Clinical Interview for DSM-IV Axis I Disorders) (First, Spitzer, Gibbon & Williams, 1999).
- SCID-II (First, Gibbon, Spitzer, Williams & Smith, 1999).

The instruments were used regardless of whether the clinical diagnosis was performed using DSM-IV-TR and/or DSM-V criteria.

Data analysis

Descriptive, bivariate and multivariate analyses were performed, and all variables are described in terms of percentages, means and standard deviations. For the

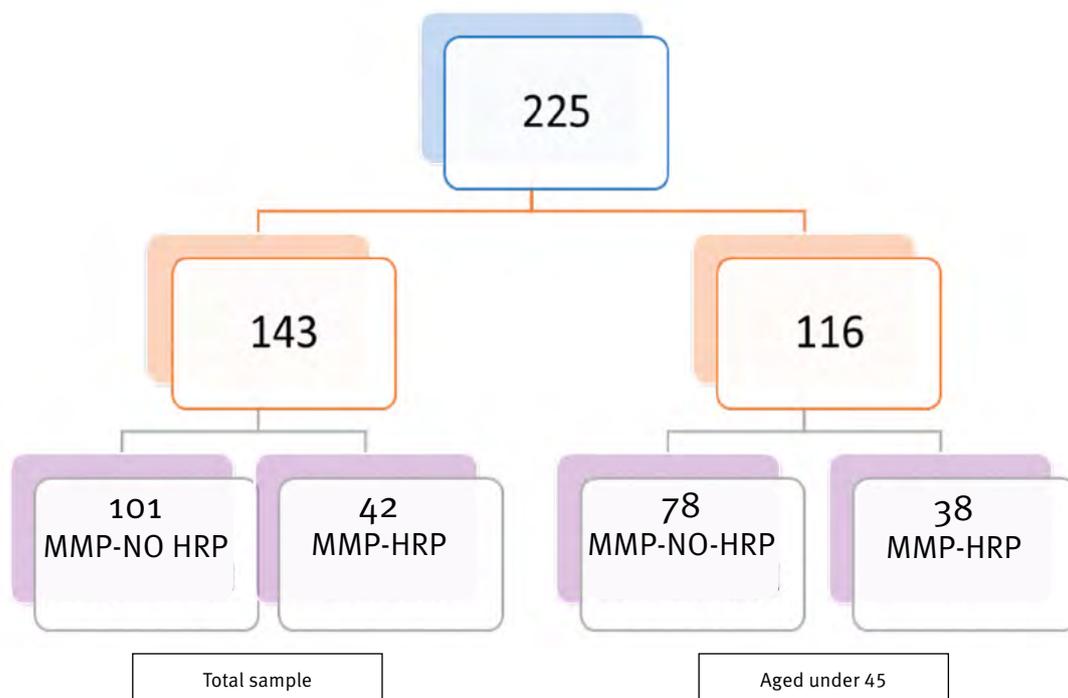


Figure 1. Patient flow.

the drugs subscale (.210 ± .159 vs .332 ± .206; $p \leq .01$) but also on the family subscale (.294 ± .292 vs .433 ± .341; $p \leq .05$). In the drug subscale, greater severity is again detected

in drug use among the MMP-HRP group. This was echoed in the family subscale, implying that MMP-HRP patients have greater drug use problems and worse family support.

Table 2. Drug use variables of the total sample.

DRUG USE RELATED VARIABLE	Total (143) M±SD	MMP-NO HRP (101) M±SD	MMP-HRP (42) M±SD	t	p
Opioid use onset age	20.52±6.60	21±7.12	19.43±5.15	1.263	.209
Opioid dependence onset age	22.42±7.52	22.76±7.70	21.73±7.18	.717	.475
Years of opioid use	11.60±8.65	11.57±8.22	11.64±9.62	.034	.973
Amount of opioids 6 months (gr/week)	.669±1.30	.701±1.40	.602±1.08	.398	.631
Amount of opioids last week (gr/week)	.655±1.21	.694±1.27	.580±1.10	.486	.628
OTHER SUD	%	%	%	X²	P
Alcohol dependence	37.8	40.6	31	1.173	.345
Cannabis dependence	30.1	29.7	31	.022	1
Benzodiazepine dependence	29.4	26.7	35.7	1.154	.316
Cocaine dependence	57.7	57	59.5	.077	.853
Tobacco dependence	84.7	87.5	78	1.977	.196
Polydrug usea	47.2	52.8	47.2	1.977	.198
Main route of opioid administration	%	%	%	X²	p
Intranasal	18.5	18.1	19.5	.039	.815
Intravenous	56.3	51.1	68.3	3.444	.089
Inhalation	3	2.1	4.9	Ns	ns
Smoked	17	22.3	4.9	6.159	<.01*
Others	5.2	6.4	2.4	Ns	ns
METHADONE	M±SD	M±SD	M±SD	T	P
Mean methadone dose	52.48±48.59	46.86±51.30	61.69±42.91	1.452	.150
	%	%	%	X ²	P
Methadone low (<40)	54.7	62.7	41.7	3.997	<.05
Methadone Medium (40-80)	29.5	25.4	36.6	1.229	.268
Methadone High (>80)	15.8	11.9	22.2	1.804	.179

Note. MMP-NO HRP = methadone maintenance program without harm reduction program; HRP = harm reduction program. M = mean; SD = standard deviation; t = Student's t; X² = chi-square; SUD = substance use disorder, ns = no statistical test, insufficient sample size. a user of opioids and other substances. *(Bonferroni correction).

Table 3. Sociodemographic and clinical variables of the under 45 sample.

SOCIODEMOGRAPHIC VARIABLES	Total (116) M±SD	MMP-NO HRP (78) M±SD	MMP-HRP (38) M±SD	t	P
Age (years)	35.52±6.28	36.54±6.10	33.42±6.19	2.572	<.05*
	%	%	%	X ²	P
Sex (male)	68.1	71.8	60.5	1.494	.289
Marital status (married)	29.7	28.4	32.4	1.02	.421
Employment (active)	12.5	12	13.5	.233	.418
Education (>High school certificate)	44.2	46.1	40.5	.306	.687
CLINICAL VARIABLES	%	%	%	X²	P
Medical history	67.3	64.9	72.2	.592	.522
Infectious diseases	38.1	35.5	45.7	1.351	.509
Hepatic diseases	40.4	38.8	58.1	5.562	.053
Psychiatric history	56.6	57.1	55.6	.025	1
Mood disorders	20.5	23	17.1	.487	.784
Personality disorders	27.7	23	40	3.385	.184
Anxiety disorders	9.7	8.7	12.9	ns	ns
Psychotic disorders	7.1	6.8	8.6	ns	ns
Induced psychotic disorder	59.4	60.9	56.3	.194	.666
Self-reference	31.8	32.7	30	.067	1
Delusion of persecution	31	35.2	23.3	1.268	.190
Hallucinations	31	33.3	26.7	.401	.626

Note. MMP-NO HRP = methadone maintenance program without harm reduction program; HRP = harm reduction program. M = mean; SD = standard deviation; t = Student's t-test; ns = no statistical test, insufficient sample size. *(Bonferroni correction).

Table 4. Drug use variables of under 45 years sample.

DRUG USE RELATED VARIABLES	Total (116) M±SD	MMP-NO HRP (78) M±SD	MMP-HRP (38) M±SD	T	P
Opioid use onset age	20.27±5.89	20.92±6.27	19±4.89	1.754	.083
Opioid dependence onset age	22.62±6.78	22.70±7.11	20.81±6.04	1.425	.158
Years of opioid use	10.49±8.10	10.16±7.50	11.06±9.14	.474	.637
Amount of opioids 6 months (gr/week)	.691±1.39	.729±1.51	.620±1.13	.387	.700
Amount of opioids last week (gr/week)	.677±1.27	.722±1.35	.602±1.15	.449	.654
OTHER SUD	%	%	%	X²	P
Alcohol dependence	38.7	41	34.2	.500	.546
Cannabis dependence	31.9	33.3	28.9	.226	6.77
Benzodiazepine dependence	31	26.9	39.5	1.888	.124
Cocaine dependence	60.3	61.5	57.9	.142	.840
Tobacco dependence	85.8	88.2	81.1	1.025	.390
Polydrug usea	49.1	53.8	39.5	2.112	.169
Main route of opioid administration	%	%	%	X²	P
Intranasal	18.9	20.3	16.2	.264	.406
Intravenous	54.1	5.9	70.3	5.876	<.05*
Inhalation	3.6	2.7	5.4	.519	.407
Smoked	18	24.3	5.4	5.977	<.05*
Others	18.9	20.3	16.2	.264	.406
METHADONE	M±SD	M±SD	M±SD	T	P
Mean methadone dose	55.30±47.20	48.17±48.78	64.66±44.05	1.502	.138
	%	%	%	X ²	P
Methadone low (<40)	50	59.5	37.5	3.524	.100
Methadone Medium (40-80)	31.1	26.2	37.5	1.084	.322
Methadone High (>80)	18.9	14.3	25	1.359	.369

Note. MMP-NO HRP = methadone maintenance program without harm reduction program; HRP = harm reduction program. M = mean; SD = standard deviation; t = Student's t; X² = chi-square; SUD = substance use disorder. a user of opioids and other substances. *(Bonferroni correction).

Table 5. Mental disorders according to SCID I and SCID II diagnoses.

Total sample	Total (143) %	MMP-NO HRP (101) %	MMP-HRP (42) %	X ²	P
Induced mood disorder	23.4	21	29.3	1.109	.381
Induced anxiety disorder	7.7	5.9	11.9	Ns	Ns
Cluster A	4.2	5	2.4	Ns	Ns
Cluster B	45.4	36	54.8	4.287	<.05
Cluster C	6.3	6	7.1	Ns	Ns
Aged under 45	Total (116) %	MMP-NO HRP (78) %	MMP-HRP (38) %	X ²	p
Induced mood disorder	22.8	19.5	29.7	1.491	.240
Induced anxiety disorder	9.5	7.7	13.2	ns	Ns
Cluster A	4.3	5.1	2.6	ns	Ns
Cluster B	44.8	38.5	57.9	3.902	<.05
Cluster C	6	5.1	7.9	ns	Ns

Note. MMP-NO HRP = methadone maintenance program without harm reduction program; HRP = harm reduction program. M = mean; SD = standard deviation; t = Student's t; ns = no statistical test, insufficient sample size. *(Bonferroni correction).

Multivariate analysis

A logistic regression analysis was performed to detect the variables related to severity in the MMP-HRP group so that all the variables of the earlier bivariate analysis that were statistically significant after the Bonferroni correction could be analyzed. For the total sample, these variables were: age, smoked route and severity of addiction on the drugs subscale. These three variables remained significant factors in the model.

For the under 45 sample, the variables involved were: age, intravenous route, smoked route and severity of addiction in drug and family subscales. Only age, smoked route and severity of addiction on the drug subscale remained significant factors in the model. Intravenous route and severity of addiction were excluded from the family subscale.

Table 6. *Addiction severity (EuropASI).*

Total sample					
EuropASI	total	MMP-NO HRP	MMP-HRP	t	p
Medical	.323±.356	.348±.364	.261±.333	1.320	.189
Employment	.612±.288	.597±.289	.651±.294	1.018	.310
Alcohol	.175±.235	.175±.238	.173±.228	.037	.970
Drugs	.253±.173	.219±.148	.333±.204	3.271	<.01*
Legal	.161±.245	.167±.250	.148±.237	.428	.670
Family	.343±.314	.318±.300	.402±.343	1.476	.142
Psychological	.331±.234	.327±.247	.341±.202	.318	.751

Aged under 45					
EuropASI	total <45	MMP-NO HRP	MMP-HRP	t	P
Medical	.301±.345	.321±.351	.261±.333	.865	.381
Employment	.617±.295	.599±.289	.655±.307	.952	.354
Alcohol	.167±.225	.163±.220	.176±.237	.300	.771
Drugs	.250±.184	.210±.159	.332±.206	3.213	<.01*
Legal	.169±.251	.175±.255	.157±.245	.356	.719
Family	.340±.314	.294±.292	.433±.341	2.277	<.05*
Psychological	.334±.236	.325±.254	.354±.197	.677	.500

Note. MMP-NO HRP = methadone maintenance program without harm reduction program; HRP = harm reduction program. M = mean; SD = standard deviation; t = Student's t; ns = no statistical test, insufficient sample size.
*(Bonferroni correction).

Table 7. *Multivariate analysis adjusted for the effect of significantly associated variables in the bivariate analysis.*

Total sample				
Variables	Wald	p	O.R.	95% IC
Age	8.87	.003	.92	.87-.97
Smoked route	5.74	.017	44.66	4.04-494.17
EuropASI drugs	9.59	.002	.14	.03-.70

Aged under 45*				
Variables	Wald	p	O.R.	95% IC
Age	4.97	.03	.92	.86-.99
Smoked route	5.35	.02	.15	.03-.75
EuropASI drugs	8.61	.00	40.36	3.42-476.84

Note. *Variable eliminated in step 2: EuropASI familial.
Note. *Variable eliminated in step 3: Intravenous route.

Discussion

There are differences between MMP patients who use harm reduction (MMP-HRP) and MMP patients who do not (MMP-NO HRP), with MMP-HRP patients being younger. There are currently no studies that specifically link this data, although some studies point to the importance of age, since younger people have less adherence to HRP programs and greater difficulty in accessing services of the same type (Krug, Hildebrand & Sun, 2015). Earlier onset and longer exposure to high-risk drug use practices among the MMP-HRP group would result in a higher risk of medical and psychiatric comorbidity (Hopfer, Khuri, Crowley & Hooks, 2002). MMP-HRP patients have a higher frequency of liver diseases (55.6% vs 38%, .053); moreover, patients over 45 years of age in this group present a significant difference (.035), which has already been described in the literature on patients using syringe

exchange programs or drug consumption facilities, who have a high prevalence of mental illness, HIV, and hepatitis C (Havinga et al., 2014; Herrero, Domingo Salvany, Brugal, Torrens & Itinere Investigators, 2011; Wang, Zhang & Ho, 2011).

Although the existence of Cluster B disorders in MMP patients is expected (Pavarsen, Masoudi, Majidi-Tabrizi & Mazhari, 2012; Roncero et al., 2016), more than half of the MMP-HRP group has one of these disorders, which can be seen as a marker of severity since personality disorders in MMP have been associated with a worse prognosis (Peles, Schreiber, Domany & Adelson, 2014). However, given that the differences are not significant we should be cautious when interpreting personality disorders.

Mental disorders in MMP patients have been associated with worse quality of life (Teoh Bing Fei, Yee & Habil, 2016), and although there are no differences between the two groups, it should be noted that in the total sample other mental disorders are highly prevalent, confirming previous findings among heroin addicts in MMP (Pavarsen et al., 2012, Pereiro et al., 2013; Roncero et al., 2016). This would indicate that the consumption of opioids is serious in itself, independently of the use of HRP resources.

Clinically, it must be stressed that more than half of the sample studied had induced psychotic disorders, with no differences between the MMP-HRP and MMP-NO HRP groups. It is not surprising that these patients suffer psychoses, since approximately 60% are also cocaine dependent, a state which has been widely associated with the presence of psychotic symptoms (Roncero et al., 2017), especially in the group of cocaine self-injectors that receive low doses of methadone (Roncero et al., 2013b). Moreover, the presence of psychotic symptoms in addicts is

a variable that affects other mental disorders with greater severity and comorbidity (Roncero et al., 2017; Roncero et al., 2013a).

In terms of the route of administration, it is already known that patients who use HRP resources tend to favor intravenous use independently of the drug involved (MacArthur et al., 2014), which is why the exchange of syringes and supervised injection facilities were the initial founding programs HRP (IHRA, 2010). Our findings corroborate this by identifying greater intravenous use (5.9% vs. 70.3%, .017) in the MMP-HRP group, while in the MMP-NO HRP group, the smoked route was preferred (24.3% vs. 5.4 %, .011). The route of administration is important because of the risks involved with intravenous use, given the greater exposure to infectious diseases (hepatitis B and C and HIV) and the medical complications that derive from these diseases (Palmateer, Kimber, Hickman, Hutchinson, Rhodes & Goldberg, 2010). Strategies are therefore needed to reduce the risk of infection and associated morbidity and mortality (MacArthur et al., 2014).

Regarding methadone dosage, it should be noted that the MMP-HRP group take higher doses of methadone compared to the MMP-NO HRP, where lower doses (less than 40 mg/day) are the norm. Yet in both groups the dosage interval is small in relation to that suggested in the literature (Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003). Low doses of methadone in the MMP-HRP group are associated with what the literature describes in a population with a harm reduction profile, where abstinence is not the main objective and the dose is part of a program with a low level of expectation typical of low-threshold MMPs (Kwan, Wong & Lee, 2015). It can be hypothesized that low doses of methadone in the MMP-NO HRP group are related to patient resistance to continue taking doses above 60 mg and the fear of complete methadone withdrawal.

The assessment of drug use severity in the MMP-HRP group through the EuropASI interview showed differences in the total sample in the drug subscale, with greater severity in the MMP-HRP group. Previous studies have already pointed to the fact that HRP patients are generally at a more severe stage of addiction (McNeil, Kerr, Pauly, Wood & Small, 2016). Furthermore, in the under 45 sample, differences were found in both the drug and family subscales, which would imply that MMP-HRP patients have less social support (Jhanjee, Lal, Mondal & Jain, 2011). This fact highlights the importance of HRP services for young patients, with greater addiction severity and less social support.

As was found in the regression analysis, MMP-NO HRP patients use other routes of administration (smoked) more frequently, implying lower risk, and the lack of family support no longer appears so relevant. The differences in variables such as age, the route of administration and

greater severity of use according to EuropASI (drug subscale) revealed by the MMP-HRP group confirm the results of previous studies indicating that patients who use HRP services are a group with greater vulnerability both at the health and social level (Havinga et al., 2014; IHRA, 2009). Although we expected the study to yield more differences between the two groups at medical and psychiatric levels, the differences found are important because the variables involved are relevant and highlight the greater severity among the MMP-HRP group, a fact that to our knowledge has not previously been described in Spain.

The limitations of the study are related to sample size, which can be explained by the complexity involved in performing a complete assessment with HRP patients. A further limitation is the methadone dosage patients receive, since it is not specified at which stage of the MMP the patients were (induction, maintenance, withdrawal). In addition, our data are not very comparable because of the lack of previous research analyzing differences between patients using MMP-HRP and MMP-NO HRP. Finally, it should be remembered that HRP programs are tools for the treatment and psychosocial support of patients with high severity and are also valued positively by the users themselves (Daigre et al., 2010) since they complement the care offered to patients who do not seek or cannot achieve total abstinence.

Acknowledgments

Elizabeth Monterde Ochoa and Thais Ballabriga (Social Educators, CAS Vall d'Hebron), Eduardo Castrillo, Miguel Angel Cantillo and Nuria Voltes Manils (Nurses, CAS Vall d'Hebron), Elena Ros-Cucurull (Psychiatrist), Constanza Daigre (Psychologist) and the whole team of the Opioid and Harm Reduction Program at CAS Vall d'Hebron, ASPB (Public Health Agency of Barcelona).

Conflicts of interest

-Dra. Nieves Martínez-Luna, declares no conflict of interest in relation to the present study, but in recent years has collaborated with Janssen-Cilag, Lundbeck and Servier.

-Laia Rodríguez-Cintas declares no conflict of interest in relation to the present study, but in recent years has received funding as a collaborator in Janssen-Cilag and Servier Laboratories projects.

-Dr. Abderramán Esojo declares no conflict of interest in relation to the present study.

-Dr. Raúl Felipe Palma-Álvarez declares no conflict of interest in relation to the present study, but has recently been a speaker in activities with Mundipharma.

-Dra. María Robles-Martínez declares no conflict of interests in relation to the present study.

-Dra. Lara Grau-López declares no conflict of interests in relation to the present study, but in recent years has collaborated with Janssen-Cilag, Lundbeck and Servier.

-Marta Perea declares no conflict of interests in relation to the present study.

-Dr. Carlos Roncero declares no conflict of interests in relation to the present study, but in recent years has received funding as a speaker and has collaborated in projects with Janssen-Cilag, Pfizer, Reckitt Benckiser/Indivior, Lundbeck, Servier, GSK, Rovi, Ferrer-Brainfarma and Astra España. He has received fees for his participation on boards of the companies Reckitt Benckiser/Indivior, Janssen-Cilag, Gilead and MSD. He has run the PROTEUS project, funded by an Indivior grant.

References

- Amato, L., Davoli, M., Perucci, C. A., Ferri, M., Faggiano, F. & Mattick, R. P. (2005). An over view of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment*, 28, 321–329. doi:10.1016/j.jsat.2005.02.007.
- Astals, M., Díaz, L., Domingo-Salvany, A., Martín-Santos, R., Bulbena, A. & Torrens, M. (2009). Impact of co-occurring psychiatric disorders on retention in a methadone maintenance program: an 18-month follow-up study. *International Journal of Environmental Research and Public Health*, 6, 2822–2832. doi:10.3390/ijerph6112822.
- Bobes, J., González, M. P., Saiz, P. A. & Bousoño, M. (1996). Índice Europeo de Severidad de la Adicción: EuropASI. Versión española. *Actas de la IV Reunión Interregional de Psiquiatría*, 201-218.
- Daigre, C., Comín, M., Rodríguez-Cintas, L., Voltés, N., Alvarez, A., Roncero, C., ... Casas, M. (2010). Users' perception of a harm reduction program in an outpatient drug dependency treatment center. *Gaceta Sanitaria / S.E.S.P.A.S*, 24, 446–452. doi:10.1016/j.gaceta.2010.09.007.
- Faggiano, F., Vigna-Taglianti, F., Versino, E., & Lemma, P. (2003). Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*, (3). doi:10.1002/14651858.CD002208.
- Fernández Miranda, J., González García-Portilla, M., Sáiz Martínez, P., Gutiérrez Cienfuegos, E. & Bobes García, J. (2001). Influence of psychiatric disorders in the effectiveness of a long-term methadone maintenance treatment. *Actas Españolas de Psiquiatría*, 29, 228–232.
- First, M.B., Spitzer, R.L., Gibbon, M. & Williams, J.B.W. (1999). *Entrevista clínica estructurada para los trastornos del eje I del DSM-IV*. Barcelona: Masson.
- First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W. & Smith, B. (1999). *Entrevista Clínica Estructurada para los Trastornos de la Personalidad del Eje II del DSM-IV*. Barcelona: Masson.
- Grau-López, L., Roncero, C., Daigre, C., Gonzalvo, B., Bachiller, D., Rodríguez-Cintas, L. ... Casas, M. (2012). Risk factors of relapse in drug dependent patients after hospital detoxification. *Adicciones*, 24, 115-122.
- Havinga, P., van der Velden, C., de Gee, A. & van der Poel, A. (2014). Differences in sociodemographic, drug use and health characteristics between never, former and current injecting, problematic hard-drug users in the Netherlands. *Harm Reduction Journal*, 11, 6. doi:10.1186/1477-7517-11-6.
- Herrero, M. J., Domingo-Salvany, A., Brugal, M. T., Torrens, M. & Itinere Investigators. (2011). Incidence of psychopathology in a cohort of young heroin and/or cocaine users. *Journal of Substance Abuse Treatment*, 41, 55–63. doi:10.1016/j.jsat.2011.01.013.
- Hopfer, C.J., Khuri, E., Crowley, T.J. & Hooks, S. (2002). Adolescent heroin use: a review of the descriptive and treatment literature. *Journal of Substance Abuse Treatment*, 23, 231-237.
- International Harm Reduction Association (2009). *Global Overview: Drugs, HIV and Hepatitis C, 2009*. Retrieved at <http://www.ihra.net/global-overview>.
- International Harm Reduction Association (2010). *What is Harm Reduction: A position statement from the International Harm Reduction Association*. IHRA Briefing, London United Kingdom, April 2010. Retrieved at <http://www.ihra.net>.
- Jhanjee, S., Lal, T., Mondal, A. & Jain, K. (2011). Heroin-dependent family: a biopsychosocial context. *Substance Abuse*, 32, 157–158. doi:10.1080/08897077.2011.558450.
- Kokkevi, A. & Hartgers, C. (1995). EuropASI: European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence. *European Addiction Research*, 1, 208-210.
- Krug, A., Hildebrand, M. & Sun, N. (2015). "We don't need services. We have no problems": exploring the experiences of young people who inject drugs in accessing harm reduction services. *Journal of the International AIDS Society*, 18, S19442. doi:10.7448/IAS.18.2.19442.
- Kwan, T. H., Wong, N. S. & Lee, S. S. (2015). Participation dynamics of a cohort of drug users in a low-threshold methadone treatment programme. *Harm Reduction Journal*, 12, 30. doi:10.1186/s12954-015-0072-z.
- MacArthur, G. J., van Velzen, E., Palmateer, N., Kimber, J., Pharris, A., Hope, V., ... Hutchinson, S. J. (2014). Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *The International Journal on Drug Policy*, 25, 34–52. doi:10.1016/j.drugpo.2013.07.001.
- Marie-Claire, C., Crettol, S., Cagnard, N., Bloch, V., Mouly, S., Laplanche, J. L. ... Vorspan, F. (2016). Variability of response to methadone: genome-wide DNA methylation analysis in two independent cohorts. *Epigenomics*, 8, 181-195. doi:10.2217/epi.15.110.

- Martínez-Luna, N., Palma-Álvarez, R. F. & Roncero, C. (2016). Reducción de Daños. E: C. Roncero & M. Casas, ed., Patología Dual, Fundamentos Clínicos y Terapéuticos, 1st ed. Barcelona: Marge Medica Books, pp.253-266.
- McNeil, R., Kerr, T., Pauly, B., Wood, E. & Small, W. (2016). Advancing patient-centered care for structurally vulnerable drug-using populations: a qualitative study of the perspectives of people who use drugs regarding the potential integration of harm reduction interventions into hospitals. *Addiction*, *111*, 685–694. doi: 10.1111/add.13214.
- Miguel-Arias, D., Pereiro Gómez, C., Bermejo Barrera, A.M., López de Abajo Rodríguez, B. Y Sobrino Prieto, M. (2016). Mortality due to acute adverse drug reactions in Galicia: 1997-2011. *Adicciones*, *28*, 80-89. doi:10.20882/adicciones.780.
- Observatorio Español de la Droga y las Toxicomanías. (2015). Informe 2015. Retrieved at http://www.pnsd.msssi.gob.es/profesionales/sistemasInformacion/informesEstadisticas/pdf/INFORME_2015.pdf.
- Palmateer N., Kimber, J. Hickman, M., Hutchinson, S., Rhodes, T. & Goldberg, D. (2010). Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. *Addiction*, *105*, 844–859. doi:10.1111/j.1360-0443.2009.02888.x.
- Parvaresen, N., Masoudi, A., Majidi-Tabrizi, S. & Mazhari, S. (2012). The Correlation between Methadone Dosage and Comorbid Psychiatric Disorders in Patients on Methadone Maintenance Treatment. *Addiction and Health*, *4*, 1-8.
- Peles E., Schreiber, S., Domany, Y. & Adelson, M. (2014). Impact of lifetime psychiatric diagnosis on long-term retention and survival of former opiate addicts in methadone maintenance treatment. *The World Journal of Biological Psychiatry*, *15*, 629-635. doi:10.3109/15622975.2014.942359.
- Pereiro, C., Pino, C., Flórez, G., Arrojo, M., Becoña, E. & COPSIAD Group. (2013). Psychiatric Comorbidity in Patients from the Addictive Disorders Assistance Units of Galicia: The COPSIAD Study. *PLoS One*, *8*, e66451. doi:10.1371/journal.pone.0066451.
- Rhodes, T. & Hedrich, D. (2010). Harm Reduction: Evidence, Impact and Challenges. EMCDDA. Retrieved at <http://www.emcdda.europa.eu/publications/monographs/harm-reduction>.
- Roncero, C., Barral, C., Rodríguez-Cintas, L., Pérez-Pazos, J., Martínez-Luna, N., Casas, M., ... Grau-López, L. (2016). Psychiatric comorbidities in opioid-dependent patients undergoing a replacement therapy programme in Spain: The PROTEUS study. *Psychiatry Research*, *243*, 174–181. doi:10.1016/j.psychres.2016.06.024.
- Roncero, C., Daigre, C., Grau-López, L., Rodríguez-Cintas, L., Barral, C., Pérez-Pazos, J., ... Casas, M. (2013a). Cocaine-induced psychosis and impulsivity in cocaine-dependent patients. *Journal of Addictive Diseases*, *32*, 263-273. doi:10.1080/10550887.2013.824330.
- Roncero, C., Fuste, G., Barral, C., Rodríguez-Cintas, L., Martínez-Luna, N., Eiroa-Orosa, F.J... Casas, M. on behalf of the PROTEUS study investigators. (2011). Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study. *Heroin Addiction and Related Clinical Problems*, *13*, 5-16.
- Roncero, C., Grau-López, L., Palma-Álvarez, R. F., Rodríguez-Cintas, L., Ros-Cucurull, E., Esojo, E. & Daigre, C. (2017). Higher severity of cocaine addiction is associated with tactile and somatic hallucination. *European Psychiatry*, *42*, 63-69. doi:10.1016/j.eurpsy.2016.11.006.
- Roncero, C., Martínez-Luna, N., Daigre, C., Grau-López, L., Gonzalvo, B., Pérez-Pazos, J. & Casas, M. (2013b). Psychotic symptoms of cocaine self-injectors in a harm reduction program. *Substance Abuse*, *34*, 118-121. doi:10.1080/08897077.2012.691446.
- Salamina, G., Diecidue, R., Vigna-Taglianti, F., Jarre, P., Schifano, P., Bargagli, A. M., ... VEdeTTE Study Group. (2010). Effectiveness of therapies for heroin addiction in retaining patients in treatment: results from the VEdeTTE study. *Substance Use & Misuse*, *45*, 2076–2092. doi:10.3109/10826081003791932.
- San, L., Arranz, B., Arrojo, M., Becoña, E., Bernardo, M., Caballero, L., ... Zorrilla, I. (2016). Clinical guideline for the treatment of dual pathology in the adult population. *Adicciones*, *28*, 3-5. doi:10.20882/adicciones.784.
- Seal, K. H., Kral, A. H., Gee, L., Moore, L. D., Bluthenthal, R. N., Lorvick, J. & Edlin, B. R. (2001). Predictors and prevention of nonfatal overdose among street-recruited injection heroin users in the San Francisco Bay Area, 1998-1999. *American Journal of Public Health*, *91*, 1842-1846.
- Teoh Bing Fei, J., Yee, A. & Habil, M. H. (2016). Psychiatric comorbidity among patients on methadone maintenance therapy and its influence on quality of life. *American Journal of Addiction*, *25*, 49-55. doi:10.1111/ajad.12317.
- Torrens, M., Fonseca, F., Castillo, C. & Domingo-Salvany, A. (2013). Methadone maintenance treatment in Spain: the success of a harm reduction approach. *Bulletin of the World Health Organization*, *91*, 136–141. doi:10.2471/BLT.12.111054.
- Wang, X., Zhang, T. & Ho, W. Z. (2011). Opioids and HIV/HCV infection. *Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology*, *6*, 477–489. doi:10.1007/s11481-011-9296-1.