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Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study

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Summary

The aim of this study was to comprehensively describe the clinical comorbidities, concomitant treatments and the current therapeutic management of opiate-dependent patients undergoing a replacement therapy programme (RTP). This is an observational, cross-sectional, multicentre, epidemiological study conducted in 74 healthcare centres for drug users. Patients were diagnosed with Opiate Dependence (OD), and enrolled in a RTP in Spain (N=624). Most patients were men (84%); they received methadone (94%) at a mean dose of 61.52mg/day during the maintenance phase, orally (95%) with take-home doses (76%). High rates of infectious (59%) and psychiatric comorbidities (67%) were found. Patients infected by HIV, HCV or coinfected by HIV/HCV were given significantly higher methadone doses ($p<0.0001$).

Key Words: opiate dependence; replacement therapies; therapeutic management; psychiatric comorbidities; infectious comorbidites

1. Introduction

Opiate dependence (OD) is defined in the DSM-IV-TR as a syndrome characterized by a maladaptive pattern of opiate use, leading to clinically significant impairment or distress [1]. In 2008 it was estimated that between 0.3% and 0.5% of the population aged 15-64 worldwide (equivalent to between 12.8 and 21.9 million people) had used opiates over the past 12 months [52], and their prevalence in Europe has been estimated to range from 0.1% to 0.8% of the population aged 15-64 [14]. Opiate consumption presents high rates of mortality and morbidity, partly because it is often associated with a wide spectrum of psychiatric and physical complications, including both infectious and non-infectious diseases, most of them requiring long-term care and management strategies [10, 11, 34, 49, 50]. The most desirable outcome in the treatment of patients with OD is their complete withdrawal from the drug. In many situations, however, this cannot be considered as the immediate goal, due to previous failures or high addiction severity. In those cases, agonist opiate therapies (otherwise called opiate replacement or substitution therapies) offer effective options, where the substitution of the opiate by another that is less addictive, provided in a strictly regulated environment, avoids withdrawal-related symptoms, prevents relapse into opiate consumption, and reduces the use of illicit opiates, as well as substantially decreasing morbidity and mortality [32, 36]. Over the years, a variety of different types of methadone maintenance programmes (MMPs) have become the mainstay of medication-assisted treatment for OD [17]. More recently, other opiate agonists, such as buprenorphine and buprenorphine/naloxone, have emerged as effective alternatives in OD treatment, as

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they are safer than methadone for use in community-based centres and more effective in the management of opiate withdrawal and maintenance [2, 26, 30, 38, 45]. Other types of medication, such as morphine and heroin, are used too, although less frequently, for stabilizing patients with OD [13, 21, 44].

Focusing now on Spain, the last Spanish Observatory on Drugs [25] reported a 0.8% life-time prevalence of heroin consumption in 2007. Besides, the number of subjects diagnosed with OD treated in various healthcare settings was 172,008 in 2008, according to the National Plan on Drugs [24]. Thus, the main OD features are well documented in Spain through the annual updates of the reports mentioned above. Other studies, however, which call into question some aspects of OD, such as the management of opiate replacement treatments, the presence of physical or psychiatric comorbidities, and concomitant treatments received by patients, are not representative of the current situation in Spain, because they rely on case reports and local investigations that were performed a long time ago, or that reported controversial results [4, 12, 16, 43, 46, 48].This study [47], therefore, was carried out to shed light on all the uncertainties referred to above that are related to the management of treatments of opiate agonists in the Spanish population of patients with OD. Furthermore, secondary objectives that fell within the scope of this study were the description of clinical (physical and psychiatric) comorbidities and their current treatment, patients' biodemographic characteristics, and familial and individual history in cases of OD (such as previous addiction treatment programmes and concomitant substance abuse).

2. Methods

2.1. *Study design and setting*

This is an observational, cross-sectional, descriptive, multicentre, epidemiological study, conducted in healthcare centres for patients with OD. Patients were recruited between September 2008 and March 2009. The Clinical Research Ethics Committee of the Vall d'Hebron University Hospital (Barcelona, Spain) approved the study, which was conducted according to the protocol and principles established by the Declaration of Helsinki, the principles of Good Clinical Practice as described in the ICH Harmonized Tripartite Guidelines on Good Clinical Practice, and the clinical guidelines for Good Epidemiological Practice [3, 29].

2.2. *Participants*

The patients recruited were adults who were at least 18 years old and had been diagnosed with OD according to DSM-IV-TR criteria, with subsequent enrolment in a replacement therapy programme in Spanish care centres for patients with OD. All the participants provided written informed consent before their inclusion.

2.3. *Variables*

Patient data were recorded in the only study visit. The main variables referred to the current therapeutic management of patients with OD, accounting for: current replacement therapy, treatment phase, dosage, time in the current replacement therapy, frequency of visits to the centre, besides the administration, presentation, prescription and delivery mode of the treatment. Secondary variables were also recorded, including: infectious and non-infectious physical comorbidities, psychiatric comorbidities according to DSM-IV criteria, concomitant treatments tailored to specific physical and mental diseases, biodemographic, personal and social data, as well as the family history for OD. Data were necessarily incomplete in the case of some variables because patients had failed to respond.

2.4. *Study size*

Since there were no *a priori* assumptions of expected percentages corresponding to each of the study variables regarding the therapeutic management of patients with OD, the maximum indetermination value was considered for the calculation of the sample size (p=0.5). Thus, in considering a total population of 83,374 patients with OD undergoing a replacement therapy programme in Spain according to the National Plan on Drugs available at the moment of designing the study [24], a sample of 760 patients provided the percentages of the different variables with a precision of 3.5% and a confidence level of 95%. These confidence and precision levels satisfied the need to ensure highly reliable biostatistical data. Assuming a 5% loss of evaluable subjects, the required total number of patients with OD was 800, a figure equal to 1% of the total subjects with OD included in replacement therapy programmes registered in Spain in 2005 (n=83,374) [24]. Lastly, in order to avoid a selection bias and secure a representative sample of the population of patients with OD in Spain, a selection of individuals was made on a proportional basis according to the number of patients with OD registered in each Autonomous

Community.

2.5. Statistical analyses

Statistical analyses were performed using the SAS programme (Statistical Analysis System), version 9.1.3. All analyses were performed using the number of valid cases (N) for each variable. Continuous variables were summarized using N, mean and standard deviation (SD), median, and extreme values. Categorical variables were described by N and percentage in each category. Variables with skewed frequency distributions were described using median and the 25th and 75th percentiles. Chi square and T tests were used to compare the characteristics of the sample when required. Univariate regression models were used to test the relationship between the methadone dose (treated as a continuous variable) and the clinical variables of interest. For all comparisons a statistical significance level of 0.05 was applied.

3. Results

3.1. Baseline sociodemographic characteristics

Table 1 summarizes the geographic distribution of researchers and the patients who were recruited.

A total of 74 researchers from 18 Autonomous Communities included 624 patients, of which 621 were evaluable. Three patients were excluded from the study because they did not fulfil the selection criteria. The sociodemographic data of the sample are detailed in Table 2.

Most patients were men (84%), with primary education (62%), unemployed (47%), receiving social support (83%) [usually from their family of origin (58%)], and without a legal history (81%). Furthermore, about half of these patients drove regularly (52%) during the study period, mainly for leisure (61%), while only about 12% of patients drove to meet work requirements. No significant differences were found in the baseline sociodemographic characteristics between OD patients in the different treatment phases (induction, maintenance, and dose reduction) [data not shown].

3.2. Therapeutic management of patients

Table 3 provides details of the therapeutic management of OD patients.

The most frequently used replacement therapy was based on methadone (94%), with a mean dose of 50.45±18.14 mg/day, 61.52±49.14 mg/day, and 29.23±29.84 mg/day in the induction, maintenance and dose reduction phase, respectively. Pa-

Table 1. Geographic distribution of the researchers and patients by Autonomous Communities (ACs).

ACs	Researchers [a] N (%)	Patients N (%)
Total	73 (100)	614 (100)
Andalucía	16 (21.9)	150 (24.4)
Aragó	1 (1.4)	10 (1.6)
Asturias	3 (4.1)	29 (4.7)
Baleares	2 (2.7)	20 (3.3)
Canarias	5 (6.8)	28 (4.6)
Cantabria	1 (1.4)	10 (1.6)
Castilla-La Mancha	2 (2.7)	20 (3.3)
Castilla y León	4 (5.5)	39 (6.3)
Cataluña	6 (8.2)	54 (8.8)
Ceuta	1 (1.4)	0 (0)
Comunidad Valenciana	4 (5.5)	37 (6.0)
Extremadura	2 (2.7)	20 (3.3)
Galicia	9 (12.3)	70 (11.4)
La Rioja	1 (1.4)	9 (1.5)
Madrid	8 (11.0)	58 (9.4)
Murcia	3 (4.1)	20 (3.3)
Navarra	1 (1.4)	10 (1.6)
País Vasco	4 (5.5)	30 (4.9)

[a] *The geographic origin of one researcher who recruited 7 patients is missing.*

Table 2. Demographic and social characteristics of the population. Patients with OD under an opiate replacement therapy (N = 621)	
Demographic data	
Age, N=566, mean ± SD	38.89 ± 7.95
Sex, N=615, men, N (%)	517 (84.1)
Social data	
Educational level, N=619, N (%)	
Uneducated	32 (5.2)
Primary	386 (62.4)
Secondary	178 (28.8)
University	23 (3.7)
Employment status, N= 576 , N (%) [a]	
Unemployed	269 (46.8)
Permanent disability/pensioner	121 (21.0)
Temporal disability	30 (5.2)
Active worker	141 (24.5)
Social support, N=587, N (%)[a]	485 (82.6)
Type of social support, N=475, N (%):	
Family of origin	276 (58.1)
Partner	178 (37.5)
Legal situation, N=609, N (%)a	
Bail / Probation	41 (6.8)
Pending trial	50 (8.2)
Without legal history	493 (80.9)
[a] *Only categories with frequencies > 5% are shown.*	

tients followed the replacement therapy for a mean of 45.88±51.86 months. The therapeutic substance was mostly delivered in the form of take-home doses (76%), usually distributed every six to seven days (55%). Lastly, visits to the centre were mainly performed as outpatient visits (96%); nearly half of these patients received outpatient visits at intervals exceeding seven days (48%).

3.3. Clinical comorbidities and concomitant treatments

Table 4 summarizes clinical comorbidities and concomitant treatments of patients.

In all, 83% of patients presented at least one clinical comorbidity. Physical comorbidities affected 69% of patients; more precisely, totals of 59% and 40% of patients presented at least one infectious and one non-infectious comorbidity, respectively. Considering all evaluable patients, the most prevalent infectious comorbidities were those involving HCV (47%), HIV (21%), and HCV/HIV (14%).

Since most patients were undergoing a methadone maintenance treatment at the time of the study (N=477), we tested the relationship between the HCV+, HIV+, and HCV+/HIV+ patients and the methadone dose received during the maintenance phase. We found a significant association between patients infected by HCV and methadone doses (F-value (F)=15.58; degrees of freedom df=1; $p<0.0001$), in such a way that HCV+ patients received an average of 17.51 ± 4.44 mg/day additional methadone dose compared with patients unaffected by HCV. Likewise, we found that HIV+ and HCV+/HIV+ coinfected patients too were receiving higher methadone doses (F=51.20; df=1; $p<0.0001$, and F=47.35; df=1; $p<0.0001$, respectively). According to our results, HIV+ and HCV+/HIV+ patients were receiving an average additional methadone dose of 35.39 ± 4.95 mg/day and 36.58 ± 5.32 mg/day, respectively. On the other hand, psychiatric comorbidities diagnosed according to DSM-IV criteria were clinically detected in 67% of patients. Further analysis were performed on the basis of a classification of psychiatric disorders according to the DSM-IV-TR axis [1] as follows: axis I, including schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, somatoform disorders, factitious disorders, dissociative disorders, eating disorders, and adaptive disorders, and axis II, accounting for personality disorders. Axis I and axis II comorbidites were found in 52% and 19% of patients, respectively.

Table 3. Current therapeutic management of patients. Patients with OD under an opiate replacement therapy (N=621).	
Current replacement therapy, N=619, N (%)	
Buprenorphine	3 (0.5)
Buprenorphine / Naloxone	29 (4.7)
Heroin	4 (0.8)
Methadone	580 (93.6)
Morphine	3 (0.5)
Phase of treatment with the current replacement therapy, N= 619, N (%)	
Induction	29 (4.7)
Maintenance	504 (81.4)
Dose reduction	86 (13.9)
Administration mode, N=620, N (%)	
Oral	590 (95.0)
Sublingual	30 (0.5)
Presentation mode, N=619, N (%)[a]	
Tablets	268 (43.2)
Solution	342 (55.2)
Other	9 (1.7)
Delivery mode, N=602, N (%)	
Take-home dose	459 (76.2)
On-site administration	134 (22.3)
Others	9 (1.5)
Visits to the centre, N=587, N (%)	
Outpatient	565 (96.1)
In-patient[b]	22 (3.9)
Current prescription mode, N=591, N (%) [a]	
Chemistry / Pharmacy	49 (8.3)
Health centre	162 (27.4)
Official narcotics prescription	162 (27.5)
Ordinary prescription	41 (6.9)
Regional AID programme	110 (18.6)
[a] Only categories with frequencies > 5% are shown. [b] Accounting for therapeutic community and detoxification units.	

Table 4. Comorbidities and concomitant treatments.Patients with OD under an opiate replacement therapy (N=621).[a]	
At least one clinical comorbidity, N=621, N(%)	514 (82.8)
Physical comorbidities, N=621, N (%)	
At least one physical comorbidity	428 (68.9)
Infectious	365 (58.8)
Non-infectious	247 (39.8)
Psychiatric comorbidities, N=621, N (%)	
At least one psychiatric comorbidity	414 (66.7)
Axis I	321 (51.7)
Axis II	116 (18.7)
Concomitant treatments, N (%)	
For infectious diseases, N=615	188 (30.6)
For non-infectious diseases, N=615	131 (21.6)
For psychiatric disorders, N=621	350 (56.4)
[a] A patient may present more than one comorbidity and receive more than one concomitanttreatment.	

Table 5. Individual and familial history of substance abuse. Patients with OD under an opiate replacement therapy (N=621)	
Duration of opiate abuse, N=563, mean ± SD (years)	18.29 ± 7.60
Family history of opiate abuse, N=617, N (%) [a]	214 (34.7)
Brother / Sister, N=197, N (%)	149 (75.7)
Father /Mother N=197, N (%)	16 (8.1)
Cousin, N=197, N (%)	16 (8.1)
Patients included in a previous replacement program classified by the current replacement therapy, N (%)	
Methadone, N=580	416 (71.7)
Buprenorphine-Naloxone, N=29	26 (89.7)
Others, N=12	10 (83.3)
a Only categories with frequencies > 5% are shown.	

3.4. *Personal and familial history of substance abuse*

Table 5 presents the personal and familial history of patients' substance abuse. A total of 35% of patients had a family history of opiate abuse, usually found in siblings (76%). When the study was conducted, 82% of the patients were abusing drugs, especially tobacco (81%). Opiates were abused by 32% of patients, mainly using heroin (27% of all patients). The leading items in the rankings for abused drugs were cannabis (50%), alcohol (42%), benzodiazepines (30%) and cocaine (29%). Most patients had been previously included in a prior replacement programme (73%) for an average of 11.58±6.03 years. The proportions of groups of patients included in previous replacement programmes revealed no differences compared with the groups of patients classified according to the replacement therapy undergone at the time of this study ($p>0.05$).

4. Discussion

The present study aimed to extensively depict the Spanish scene with respect to the therapeutic management and the characteristic profiles of patients with OD included in opiate replacement programmes. Most patients were men (84%), had undergone their replacement therapy in a maintenance regime (81%), had received methadone (94%) at a mean dose of 61.52 ± 49.14 mg/day during the maintenance phase, and presented high rates of infectious (59%) and psychiatric comorbidities (67%). Moreover, we found an association between the infectious comorbidities and the methadone dose received.

Although there are few examples in the literature of studies that aimed to investigate as their main objective the profile of OD patients taking opiate substitutes, the sociodemographic characteristics of patients included in our study (mainly men [84%], young adults [38.89 ± 7.95 years old], with primary education [62%], receiving social support [83%], without legal history [81%], and mostly classified either as unemployed [47%] or as active workers [25%]) resemble those previously reported. For example, Domingo-Salvany *et al*. [12] illustrated the methadone treatment network in Spain in 1994 through a sample of over 13,000 patients with a mean age of 28.5 years (ten years younger than our population) and a percentage of men as high as 79%. Other studies exploring smaller cohorts of Spanish patients with OD receiving opiate replacement therapies likewise reported a majority of men (between 77% and 95%), with a mean age ranging between 31 and 42 years old, with primary education (range: 40 to 77%), unemployed (range: 40 to 59%), and without legal history (range 44% to 77%) [5, 19, 40, 41]. When considering other countries apart from Spain, similar results are found (most patients being males, young adults, unemployed, without legal history and nearly half of them having primary education only) [10, 11, 22, 49, 54, 55]. However, Quaglio *et al*. [42] reported a cohort of OD in Italy with higher levels of social integration: only 16% of patients were unemployed, 80% had an educational level extending beyond primary education, and 50% of patients were living with their parents. In our study, most patients also received social support, which mainly came from their family of origin (58%), although this was not the situation found in another European study, where only 5% of patients lived with friends, parents or relatives [54]. Lastly, to our knowledge, this is the first study to provide a detailed inquiry into the proportion of regular drives in a large set of patients with OD receiving opiate agonists (52%). Generally speaking, our study mainly coincides with the baseline characteristics of OD patients undergoing opiate agonist treatments, as reported in most of the studies mentioned above [5,

10, 11, 19, 22, 40, 49, 54, 55], so making it possible to compare our results with earlier ones that deal with the therapeutic management of opiate replacement programmes, clinical comorbidities and the history of OD.

Going on now to the management of replacement therapies, methadone was the most frequent opiate agonist used in our study, with only 4.7% and 0.5% of patients receiving buprenorphine/naloxone and buprenorphine, respectively. This does not reflect the current situation in most countries in Europe, since high-dosage buprenorphine, for example, is now available in all but four European Union member states (including Spain), and is used in a fifth to a quarter of all the substitution treatments provided all over Europe [14]. Moreover, although the buprenorphine/naloxone combination was approved by the European Medicines Agency in 2006, and introduced in 14 countries [14], after becoming commercially available in Spain in 2008, it was only financed by the Spanish National Health System at the end of 2009. As a result, that combination is, in all probability, prescribed to more patients now than it was when the present study was being conducted, due to their reportedly high effectiveness in treating OD and reducing intravenous misuse [30, 38]. On the other hand, the average methadone dose received during the maintenance phase by our patients was 61.52 mg/day, a figure very close to that being prescribed almost 14 years ago in Spain (60 mg/day), according to the study of Domingo-Salvany *et al*. [12], and a little higher than the doses currently being prescribed during the maintenance phase in four European countries (44.3 mg/day) [6]. In the United States, Pollack *et al*. [39] reported that, in 2005, 44% of patients received methadone doses of at least 80 mg/day, and 34% below 60 mg/day**,** stating that one third of methadone facilities provided doses below recommended levels. Methadone dosing is a crucial treatment characteristic, with a general recommendation for methadone dosing during maintenance treatment to fall within a range going from 60 to 120 mg daily, since excessive opiate dosing can lead to overdoses and/or death, whereas doses that are too low may limit the potential for treatment success and favour the continuation of illicit drug use, together with its harmful consequences [15, 35]. Hence, the methadone doses received in our study fell at the lower end of the acceptable range. It is worth mentioning too that in Spain the prescription of low methadone doses is not an outcome of economic factors, unlike the situation in other countries, such as the United States, where financial factors constitute the main reason why methadone doses are prescribed at below recommended levels [39]. Lastly, while methadone has been reported to be often administered orally, once daily, and as a solution [56], very few studies have aimed to give comprehensive details on the administration, presentation, delivery and prescription mode of opiate agonists in Spain. In our study, subjects were mainly asked to visit the centre as outpatients there (96%), and took the opiate agonist orally in the form of take-home doses (76%) that were usually supplied every six or seven days (55%), a technique that has been widely reported to improve patients' quality of life and their retention in treatment [8, 23].

Besides this, although 73% of patients had previously attended replacement therapy programmes over an average time-span of 12 years, the drug abuse in our sample was long-standing (18 years, on average) – a finding that mainly reflects the chronicity and severity of the addiction. Moreover, we found a widespread concomitant use of other substances, with a large proportion of patients (82%) who abused drugs, including tobacco, cannabis and alcohol, in addition to heroin or other opiates, which could partly account for the low methadone doses received [51]. Furthermore, prescribed drugs such as benzodiazepines were also found to be commonly abused, as previously reported in another Spanish population of OD patients [41]. All in all, these results indicate that severe addiction features in our sample of patients with OD in a way reminiscent of that reported in previous studies, presenting, for instance, similar (25-29%) [27, 57] or lower (<8%) [7, 9, 28] rates of concomitant opiate abuse.

As to physical comorbidities, Domingo-Salvany *et al*. [12] identified 60% of OD patients treated with opiate agonists infected by HIV in 1994, while more recent studies have described a lower proportion of HIV+ patients (approximately 25%) in agreement with our findings [5, 40]. Accordingly, we found that a high proportion of patients had concomitant infectious diseases, mainly HCV (47%), HIV (21%) or a combination of both (14%). The prevalence of these associated infectious diseases in OD patients has fallen in the past few years mainly due to a decline in injecting drug use, and availability of prevention, treatment and harm reduction measures, including substitution treatment, and needle and syringe programmes [14]. Moving on now to the question of psychiatric comorbidities, several previous studies have described high rates of dual diagnosis (understood as comorbidity between substance use disorders and other psychiatric disorders), ranging between 44% and 93% [31]. When focusing on Spain, a similar scenario is found, and a great degree of variability is reported in the co-occurrence of OD and other psychiatric

disorders [4, 16, 43, 48]. These controversial results can be accounted for in terms of population bias, local bias, small sample sizes, opiate agonist treatments received, or psychometric instruments employed. In the present study, however, we interrogated a representative sample of Spanish patients with OD treated with opiate agonists and were able to confirm the high incidence of dual diagnosis (67%). In addition, while other studies found a prevalence of personality disorders among OD patients ranging between 35% and 65%, we found a lower prevalence (19%). In any case, this kind of assessment is very important, since personality disorders might well influence the prognosis of OD and its treatment [18].

Lastly, it turned out that infected patients were receiving significantly higher methadone doses in the case of HIV, HCV, and HIV/HCV coinfection. Higher methadone doses are associated with increased treatment retention, less risk of relapse and its negative consequences in terms of drug use, and a lower incidence of infections [15, 8, 53]. Accordingly, we hypothesised that patients receiving higher methadone doses were those showing greater severity of addiction, though in the case of infectious comorbidities the data might be explained by the need to increase the methadone dose in patients taking antiretrovirals due to its effect on cytochrome p450 [20, 33, 37]. One of the main strengths of our study is that patient recruitment was delegated to 18 Autonomous Communities and various types of health centres providing opiate replacement therapies. As a result it was focused on a highly representative sample of the Spanish population suffering from OD and under treatment with opiate agonists. An additional advantage of this procedure was that selection bias was precluded. In this way, all the data collected that referred to replacement therapy programmes in our sample are of particular value, as they cover a therapeutic area of OD never fully explored until now in the Spanish population. Besides this, to our knowledge, this is the first study that has reported a high prevalence of dual diagnosis in a large Spanish sample of patients with OD. On the other hand, our study had some limitations. First, instead of the initial figure of 760 patients that had been calculated to ensure a precision of 3.5% in the 95% confidence intervals, the eventual sample size was 621 patients, which could mean a slight loss of precision in the statistical analyses. Even so, since the main aim was a descriptive analysis of the therapeutic management side, this would not affect the major outcomes. Second, as most of the assessed patients were polydrug users, sample heterogeneity was another constraint that was insurmountable, due to the very nature of the sample studied. Finally, data collection was obtained through direct interview without using standardized protocols; consequently, a recall bias cannot be ruled out.

Overall, the present work gives a clear and representative picture of the therapeutic management of subjects with OD undergoing an opiate replacement therapy in Spain, while bringing out the importance of exploring in detail the profiles of patients who make up large samples. This could represent a step further towards a more appropriate and effective management of opiate agonist treatments – an objective which might, in its turn, lead to better treatment outcomes.

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Appendix A. The PROTEUS study group.

The following researchers have participated in the PROTEUS study: Addis Leonor de Álava Gelso, Aimee María Ruiz Rodriguez, Alfredo Gurrea Escajedo, Amhed Fabelo Laza, Ana Aparicio Aparicio, Ana Mª Fernandez Sobrino, Ana Maria Germain Estebanez, Antonio Terán Prieto, Arancha López Mariano, Ariadna Balagué Añó, Bartolomé Baena San Juan, Bartolomé de la Fuente Darder, Begoña de Pablo García, Carlos Muralles Jiménez, Carlos Murga Cerviño, Carmen Beltran Porter, Carmen Cortell Cortell, Carmen Iglesias Azcue, Carmen Puerta García, Daniel Ángel Pereda Beaure, Desiderio Mejías Verdú, Francisco J. Samper Villar, Francisco Luque García, Garbiñe Caminos Valencia, Gemma Isabel San Narciso Izquierdo, Javier Ogando Rodríguez, Joaquín Martínez Valente, José A. González Aragón, José Antonio Segura Zamudio, Jose Luis Navarro González, José Manuel Fernández Fernández, José Martínez Raga, José Miguel Zoido Ramos, Juan Jesús Ruiz Ruiz, Juan Manuel Jiménez Lerma, Juan Ramírez López, Lucía Yolanda Armenteros García, Luis Garau Perello, Manuel Ruiz Martínez, Marco A. Rovira Isanda, Margarita Rossello del Rosal, María Elena Barbero García, María Olga Chapinal Sánchez, Mª Carmen Romero Truño, Mª Jesús Longo García Peñuela, María del Carmen García Nicolás, María del Mar Sánchez Fernández, María Jesús Antuña Díaz, María Lizaur Barbudo, María Paz Mateos Ayucar, Oscar Galera García, Pablo Vega Astudillo, Pedro A. de Armas Espinosa, Pedro Galindo Espada, Pilar Garzon Nacher, Rafael Forcada Chapa, Ricardo Ortega García, Ricardo Testa Garrido, Roberto Amador Curbelo, Roberto Fernando Artabe Noya, Tomás Díaz González, Tre Borras Cabaces, Víctor Puente Pazos, and Visitación Villafuertes Márquez.

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Contributors

Dr. Carlos Roncero and Dr. Miguel Casas designed the study and wrote the protocol. The PROTEUS GROUP, visited the patients and collected patient´s data for the study.

Laia Rodriguez-Cintas, Dr. Nieves Martínez-Luna, Francisco Jose Eiroa-Orosa participated in the statistical analysis and interpretation of the results. Dr. Roncero, Dr. Fusté, and Dr. Barral wrote the first draft of the manuscript and all the authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Roncero has received honoraria for speaking for: Janssen-Cilag, Bristol-Mayers Squibb, Pfizer, Reckitt Benckiser, Lundbeck, Servier and Adamed Spain; and he has received fee for participating as a member of the Janssen-Cilag board. Dr. Fusté has received honoraria for speaking for Bristol-Myers Squibb, and has received funds from Pfizer, Wyeth, Sanofi and AstraZeneca for financing further Psychiatry training. Dr. Barral has collaborated as speaker for Bristol-Myers Squibb, and has received funds from Adamed for funding a Mentalization Based Therapy Training. Dr. Casas has received funds from Janssen-Cilag, Pfizer, Adamed, Reckitt Benckiser and AstraZeneca laboratories and he has received fee for participating as a member of

the Janssen-Cilag board. All the other authors declare that they have no conflicts of interest.

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