Psychiatric comorbidities in opioid-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study

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Psychiatric comorbidities in opioid-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study.

Running head: Dual diagnosis patients in Spanish OAT programmes

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Abstract

Opioid-dependent patients show a high rate of psychiatric comorbidities. The prevalence and characteristics of patients with dual diagnosis have not been well established in Spanish opioid agonist treatment (OAT) programmes. Thus, 621 opioid-dependent patients enrolled in OAT programmes were assessed, using the EuropASI questionnaire, for psychiatric comorbidities, which were detected in 67% of patients (anxiety 53%, mood disorders 48%, sleep disorders 41%, substance-related disorders 36%). In addition, compared with patients without a dual diagnosis, patients with dual

pathology were significantly older, used benzodiazepines and cannabis in significantly greater percentages, and showed significantly more frequent infectious and non-infectious comorbidities, worse overall working status, a lower proportion of drivers and higher levels of severity regarding medical, employment, alcohol, legal, family and psychological issues. Therefore, the data showed a very high prevalence of psychiatric comorbidity in opioid-dependent patients receiving OAT in Spain and several problems frequently associated with patients with dual diagnosis. Physicians treating opioid-dependent patients should be aware of these facts to correctly identify and manage patients with a dual diagnosis.

Key-words: opioid dependence; opioid agonist treatment; dual diagnosis; methadone; psychiatric; comorbidity; EuropASI questionnaire.

1. Introduction

Clinical and epidemiological studies have revealed a high and broad rate of comorbid psychiatric disorders (44-93%) in opioid-dependent (OD) patients (Mateu et al., 2005), including those with prescription opioid dependence (Gros et al., 2013; Pereiro et al., 2013). In a Spanish sample of OD patients in a methadone maintenance programme (Astals et al., 2009), 32.3% had co-occurring mental disorders or a dual diagnosis (over half of them with Axis I disorders alone), and the prevalence seems to be increasing with time (Sanvisens et al., 2014).

The different diagnostic criteria used in the studies are probably the major contributor to the large variability in the reported prevalence (Mateu et al., 2005; Nunes and Rounsaville, 2006; Schuckit, 2006). However, a high prevalence of psychiatric comorbidities, especially depressive, anxiety, and personality disorders, in OD population, is well established (Haro et al., 2004; Roncero et al., 2012; Strain et al, 2002; Wu et al., 2013). The presence of previous mental disorders has been shown to be a predictor of incident substance use/dependence (Katz et al., 2013; Maremmani et al., 2011a; Reidy et al., 2014). However, substance use may also be cause of inducing psychiatric disorders, such as stimulant- or drug-induced psychoses and substance-induced mood disorders, as well as substance-induced anxiety conditions (Maremmani et al., 2011a; Schuckit, 2006).

Overall, OD patients seeking treatment show a poor quality of life (QoL) (Astals et al.,

2008), which seems to be worse in those with a dual diagnosis (Bizzarri et al., 2005; Fassino et al., 2004; Iskandar et al., 2013). Thus, the need to treat concomitant mental disorders must be emphasized in patients receiving OD treatment. The importance of assessing psychiatric comorbidities in these patients has further implications because these comorbidities seem to have a certain influence on costs (Roncero et al., 2015) as well as on treatment outcomes and patients QoL. In fact, some psychiatric symptoms in OD patients are associated with drug misuse and thus show rapid remission after drug-dependence treatment (Gossop et al., 2006). Furthermore, it seems that patients with dual diagnosis on methadone treatment show better outcomes than OD patients with no psychiatric comorbidities (Maremmani et al., 2013; Ngo et al., 2011), although the additional medication for the treatment of psychiatric symptoms might partly explain these more positive outcomes (Maremmani et al., 2013). In addition, opiate treatment can have a different outcome not only in patients with or without dual diagnosis but also, depending on the specific type of treatment, a more or less pronounced effect in different groups (Schafer et al., 2010).

The available studies in Spain regarding patients with dual diagnosis are scarce, and thus more studies should be conducted to characterize this group of patients. With this aim in mind, we proceeded to assess the psychiatric comorbidities of a large OD population enrolled in opioid agonist treatment (OAT) programmes in Spanish care centres and to compare the different sociodemographic (including gender) and clinical characteristics (including severity and type of treatment used) according to the presence of at least one comorbid psychiatric disorder (i.e., whether patients had or did not have dual pathology), with specially focus on mood, anxiety and sleep disorders due to their high frequency among patients with dual pathology and on psychotic disorders due to their severity.

2. Methods

2.1. Patients and variables

The methods are described in detail in (Roncero et al., 2011). The PROTEUS study was an observational, cross-sectional, descriptive, multicentre, epidemiological study conducted in healthcare centres for patients with OD. The study was approved by the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital (Barcelona, Spain), and it was conducted according to the Declaration of Helsinki (Tokyo, 2004).

Patients who were at least 18 years old, diagnosed with OD according to the DSM-IV-TR criteria (American Psychiatric Association, 2000), and enrolled in an OAT programme in a Spanish care centre for patients with OD were recruited. The patient recruitment was performedin proportion to the number of patients with OD registered in each Autonomous Region between September 2008 and March 2009. Each participant provided written informed consent before inclusion.

Patient data were recorded at a single study visit with a one-hour duration. All physicians received instructions on performing the diagnosis based on patient history according to the DSM criteria and on collecting the data. Additionally, they were trained to administer the EuropASI interview. The main variable, the current therapeutic management of patients with OD enrolled in a replacement therapy programme, has been described elsewhere. The secondary variables included the description of physical and psychiatric comorbidities. Psychiatric comorbidities were diagnosed according to the DSM-IV-TR, and their distributions according to gender and to methadone dose were assessed. The Spanish translated and validated version of the EuropASI questionnaire (Bobes et al., 2007; EUROPASI, 1994; Roncero et al., 2011) was used to assess the dependence severity and related problems in a face-to-face interview conducted by a trained interviewer. The EuropASI is a semi-structured interview that collects information about general medical status, occupational and economic status, alcohol consumption, consumption of other drugs, legal problems, family and social relationships, and psychological status. The composite score used range from 0 to 1, with higher scores indicating greater severity. The EuropASI can be used to assess the severity of the patient's problems and, with periodic repeated administrations, to monitor and quantify the changes in problems commonly associated with substance abuse. One of its limitations is the time needed to perform the interview as well the necessity to have the patients' cooperation. In section I, psychiatric status and mood and psychotic disorders were analysed according to the patient's perceptions and the doctor's clinical perceptions. A patient was considered to have a mood disorder if, on the EuropASI section I, patient items 3 (Experienced serious depression), 9 (Experienced serious thoughts of suicide) and 10 (Attempted suicide) and interviewer items 14 (Obviously depressed/withdrawn) and 19 (Having suicidal thoughts) were marked in the clinical report form (CRF). A patient was considered to have a psychotic disorder if patient item 6 (Experienced hallucinations) and interviewer item 17 (Having trouble with reality testing, thought disorders, paranoid thinking) were marked.

2.2. Statistical methods

Continuous variables were described using measures of central tendency, and T-tests were used to compare the characteristics of the sample. For categorical variables, the chi-square test was used, except when at least one box displayed an expected frequency of less than 5, in which case Fisher's correction was applied. All analyses were performed using the number of valid cases (*N*) for each variable. To reduce false positives, Bonferroni correction for multiple tests was performed. Statistical analyses were performed using SAS (Statistical Analysis System), version 9.1.3. A statistical significance level of 0.05 was used for all comparisons.

3. Results

3.1. Overall patient characteristics

A total of 624 patients from 74 centres were enrolled, and 621 were analysed because 3 did not meet the study inclusion criteria (Roncero et al., 2011).

The sociodemographic and clinical characteristics of the study population have been previously described (Roncero et al., 2013; Roncero et al., 2011). Overall, the mean age was 38.9 years, 84% were men, 47% were unemployed, 19% had legal problems, and 52% drove regularly. Most (94%) were being treated with methadone, 59% had infectious comorbidities [mainly Hepatitis C Virus (HCV) and/or Human Immunodeficiency Virus (HIV)], and 66.8% had psychiatric comorbidities. When the study was conducted, 82% of patients still abused drugs, mainly tobacco at 80.8% (93.3% of patients who still abused drugs), followed by alcohol at 57.6%, cannabis 59.5%, cocaine 36.9%, heroin 36.9%, benzodiazepines 33.9%, and opioids 7.45%.

3.2. Psychiatric comorbidities

As mentioned in section 3.1, psychiatric comorbidities were clinically detected in close to 67% of all evaluated patients. The most frequent were anxiety (53%) and mood disorders (48%), followed by sleep disorders (41%), substance-related disorders (36%), and personality disorders (27%). Impulse-control disorders not elsewhere classified were observed in 16% of patients, schizophrenia and other psychotic disorders in 12%, and other disorders were present in smaller percentages.

Women had significantly more sexual and gender identity disorders than men (6% versus 2%, respectively; p=0.0316) but significantly less schizophrenia and other psychotic disorders (3% versus 13%; p=0.0226). (**Table 1**).

The proportion of patients with at least one psychiatric comorbidity increased significantly with methadone dose (p=0.0066) due to the group with substance-related disorders, which was the only psychiatric comorbidity that increased with methadone dose (p=0.0109) (**Table 2**). The only disorder group associated with leaving an OAT programme was personality disorders, which was more frequent among patients who had left previous OAT programmes than among those who had stayed (46% versus 26%, respectively, p=0.0175) (data not shown). Only 29 patients (4.7%) received buprenorphine-naloxone (B/N), and they experienced less sleep disorders (19% vs. 43%, respectively; p=0.0327) but more infancy, childhood, and adolescent disorders (19% vs. 5%; p=0.0093) and personality disorders (57% vs. 26%; p=0.0015) than those who did not receive B/N (data not shown).

3.3. Comorbidities on axis I and II

Axis I comorbidities were found in 51.7% of patients, usually one (48%) or two (41%) comorbidities, while 18.7% of patients had at least one comorbidity on axis II (data not shown). No significant differences were found in the proportion of patients with axis II comorbidities according to the presence of axis I comorbidities. In addition, no significant differences were found in patients with at least one axis I comorbidity (nor according to the number of comorbidities) or axis II comorbidity according to age, gender or history of previous rehabilitation programme.

3.4. Mood and psychotic disorders

Psychotic disorders were about half as frequent as mood disorders, both according to patient's and to doctor's opinions (**Fig.1**).

High concordance was observed between patient's and doctor's perceptions regarding negative mood as well as negative psychotic cases, but low concordance was observed regarding positive cases. In 54% of patients reporting mood disorders and 67% of patients reporting psychotic disorders, there was no medical confirmation. Patients

treated for OD who reported concomitant cocaine abuse showed significantly more psychotic disorders in the last month than those treated for OD only (6% versus 1%, respectively; p=0.0004) (data not shown).

One percent of patients had attempted suicide in the last month (22% lifelong), and 2% had experienced hallucinations in the last month (27% lifelong).

3.5. Comparison of patients with dual vs. patients without dual diagnoses

Patients with dual pathology were significantly older (p=0.007), showed infectious and somatic comorbidities in greater percentages ($p\leq$0.0001), and used benzodiazepines ($p\leq$0.0001) and cannabis (p=0.046) more frequently than patients without dual pathology (**Table 3**). Significant differences between groups were also observed in working status ($p\leq$0.0001), with larger percentages of patients with dual diagnosis showing temporary as well as permanent disability and a lower percentage actively working compared to those without dual diagnosis, and in driving status, with a smaller proportion of drivers among patients with dual than among those without dual disorders ($p\leq$0.0001). Patients with dual pathology showed more (and with higher levels of severity) medical ($p\leq$0.0001), employment (p=0.010), alcohol ($p\leq$0.0001), legal (p=0.009), family ($p\leq$0.0001) and psychological issues ($p\leq$0.0001) than patients without dual disorders. No significant differences were observed regarding gender, education level, enrolment in a previous OAT programme, family history of opioid consumption, current drug consumption, and degree of severity of drug problem.

Significant differences between patients with specific dual diagnosis and the rest of the study population are shown in **Table 4**. Patients with mood, anxiety and sleep disorders used benzodiazepines more frequently than other OD patients ($p\leq$0.0001). Overall, patients in all specific groups reported a worse working status and significantly ($p\leq$0.05) larger proportions of patients with different problems –according to the medical, employment, alcohol, legal, family and psychological EuropASI subscales - and with a greater degree of severity than the rest of the study population (data not shown). It should be noted that psychological problems included any type of serious psychiatric symptoms and treatment for any type of psychiatric problems.

3.10. Dual diagnosis and treatment

Fifty-six percent of patients had received pharmacological treatment for psychiatric comorbidities at least once. The most frequent treatments were benzodiazepines (67%) and antidepressants (62%).

4. Discussion

Previous studies have revealed a high rate of psychiatric comorbidities in OD patients (Mateu et al., 2005; Pereiro et al., 2013; Schuckit, 2006; Strain, 2002) and a higher risk of experiencing these psychiatric disorders compared to the general population (Fan et al., 2014). However, there were few available data regarding this issue in Spain, and thus we aimed to determine the prevalence of dual diagnosis among OD patients in OAT programmes; our analyses showed a high rate of dual diagnosis at 66.8%.

A high prevalence of psychiatric comorbidities among OD patients has been observed in previous Spanish studies. A study conducted in Barcelona showed that 67.1% of young adult heroin and/or cocaine users recruited in nonclinical settings suffered from a lifetime psychiatric comorbidity (Rodriguez-Llera et al., 2006) and showed incidences of new substance use disorders (SUDs) and non-SUD Axis I disorders of 18% and 11%, respectively, at 18 months (Herrero et al., 2011). In Galizia, 56.3% of patients treated in addictive disorder assistance units were patients with dual diagnosis (Pereiro et al., 2013). A small study conducted in Barcelona with patients in an OAT programme showed a 32.3% prevalence of psychiatric comorbidity (Astals et al., 2009) and a cumulative incidence of co-occurring disorders of 13% during the 18-month follow-up period. In Madrid, the prevalence of dual disorders, excluding nicotine dependence, was reported to be 61.8% (Arias et al., 2013). The different prevalence data observed in the mentioned studies might be partly explained by differences in the study design, the questionnaires used to assess psychiatric comorbidity and the characteristics of the study population.

As expected, patients with dual diagnosis showed a worse employment status and more severe medical, employment, alcohol, legal, family and psychological problems than patients without dual diagnosis. These data agree with previous studies, which also reported higher problem severity scores in OD patients with comorbid psychiatric disorders (Carpentier et al., 2011), including prescription OD patients with dual diagnosis (Griffin et al., 2014). In addition, patients with dual diagnosis overall reported abusing other substances (benzodiazepines and cannabis) more frequently than patients

without other diagnoses, confirming previous observations (Carpentier et al., 2009; Carpentier et al., 2011; Savant et al., 2013; Wedekind et al., 2010).

In agreement with previous similar studies (Carpentier et al., 2009; Darke et al., 2015; Pereiro et al., 2013; Rodriguez-Llera et al., 2006; Savant et al., 2013; Strain, 2002; Yin et al., 2015), mood and anxiety disorders, as well as personality disorders, were the most frequent psychiatric comorbidities. The prevalence of mood disorders was 48%, slightly above the 45% lifetime prevalence of this type of psychiatric disorder observed in a previous study conducted in patients seeking B/N treatment (Savant et al., 2013). In the mentioned study, which was conducted in Galizia (Pereiro et al., 2013), mood (22.3%), personality (20.5%) and anxiety disorders (14.3%) were also the most frequent types, although at lower rates than in the current study. However, the study was conducted in 6 alcoholism units in addition to 17 drug dependency units and included patients with abuse of different substances. Mood disorders were also less frequent (26%) in a study conducted in Barcelona, but the differences in population characteristics and assessment methods might explain that lower rate (Rodriguez-Llera et al., 2006). In fact, their population was younger than ours, patients were recruited from non-clinical settings, 71% were cocaine dependent (7% as the only diagnosis and 64% in addition to OD), and the PRISM, rather than the EuropASI, was used to assess their psychiatric disorders.

Psychotic disorders were more frequent in patients treated concomitantly for cocaine abuse, in agreement with previous studies showing an association between manic episodes and the use of CNS stimulants (Dalmau et al., 1999; Maremmani et al., 2012; Schuckit, 2006) and specifically between psychotic symptoms and the use of cocaine (Roncero et al., 2014a; Roncero et al., 2014b). Additionally, there were more men with psychotic disorders, while women suffered more frequently from sexual and gender identity disorders, consistent with previous studies in OD patients that showed an association between certain psychiatric disorders and gender. Overall, women are more likely to suffer from mood and anxiety disorders than men (Daigre et al., 2015; Herrero et al., 2011; Mezzatesta-Gava et al., 2014; Peles et al., 2007; Wedekind et al., 2010). In addition, when women are diagnosed with Axis II disorders, these are most likely to be cluster C personality or paranoid disorders, while men are more likely than women to be diagnosed with antisocial personality disorder (Grella et al., 2009; Mezzatesta-Gava et

al., 2014). However, our results regarding women should be interpreted with caution because we had a low percentage of female participants (typical for this patient population), which could preclude a detailed comparison of some specific diagnoses.

Sleep disorders were also quite frequent (41.4%). Sleep apnea is a well-known adverse effect of long-term opioid use (Walker et al., 2007), and sleep disorders have been observed in multiple studies in OD patients undergoing OAT programmes and in patients using or abusing prescription drugs (Hartwell et al., 2014; Liao et al., 2011; Morasco et al., 2014; Pud et al., 2012; Rose et al., 2014; Sharkey et al., 2010, 2011). Some of these previous studies have shown that 65-75% of patients in OAT and 35.7% of prescription OD patients reported sleep difficulties as their reason for prescription drug use (Barth et al., 2013; Nkire et al., 2013; Peles et al., 2006).

There were proportionally fewer drivers among patients with than in those without dual diagnosis, specifically in patients with mood, anxiety or sleep disorders. The effects of OAT on patient´s driving ability are controversial (Baewert et al., 2007; Fishbain et al., 2003; Loeber et al., 2012; Schindler et al., 2004). Although OAT might impair driving ability, it does so to a less degree than other psychotropic agents or drugs of abuse (Soyka, 2014). Still, many patients on OAT do not drive (Roncero et al., 2013). On the other hand, patients with anxiety or mood disorders, as well as patients with any type of sleep disorder, have shown an increased risk of collision (Boivin and Boudreau, 2014; Johnson et al., 2014; Karimi et al., 2014; Wickens et al., 2013). Thus, not surprisingly, patients who exhibit two risk factors for poor driving and accidents will want to drive less than patients with only one risk factor.

Regarding physical comorbidities, patients with dual diagnosis showed about twice more comorbidities (1.6 times as many infectious comorbidities and 2.3 times as many other somatic comorbidities) than patients without. Recent multiple logistic regression analyses conducted in over 34,000 subjects twenty years or older showed that having a physical condition, as well as having an Axis I or II mental disorder, was a predictor of incident nonmedical prescription opioid use and later opioid abuse/dependence (Katz et al., 2013). Adjusting for sociodemographics and Axis I and II conditions, that same study showed that having any chronic physical condition, except for gastrointestinal disease, was a predictor of OD, with cardiovascular disease having the strongest

association with OD (Katz et al., 2013).

Fifty-six percent of the study patients received at least one treatment for psychiatric comorbidities. As the percentage of affected patients was 66.8%, this implies that psychiatric comorbidities were undertreated, given the 12% of patients who had not received pharmacological treatment specifically targeting the comorbidity and probably a greater percentage of patients receiving partial treatment for the comorbidity.

Although it is not possible to know if the opiate dependence occurred before or after the other psychiatric disorders, given the cross-sectional nature of the study, and although it is not possible to know if the opiates were used to treat other comorbidities, it has been suggested that OD treatment alone might be sufficient to control psychiatric symptoms (Strain, 2002) because in patients with dual diagnosis, OAT might also be effective in preventing mental disorders (Maremmani et al., 2011b; Maremmani et al., 2014a; Maremmani et al., 2014b). Furthermore, patients with dual pathology may experience better outcomes than those without additional pathology regarding several treatment outcomes. In a previous study conducted in OD patients undergoing treatment, drug-related hospitalizations consistently decreased following treatment in patients with dual pathology, while it increased in those with no psychiatric comorbidity (Ngo et al., 2011). When OD patients were included in a high-threshold, maintenance-oriented, high-dose methadone programme, those with comorbid bipolar 1 disorder showed better long-term outcomes than those without psychiatric comorbidities (Liao et al., 2013; Maremmani et al., 2013), and of heroin addicts who also met the criteria for treatment resistance, those with DSM-IV axis I psychiatric disorders showed better outcomes than those without such comorbidity (Maremmani et al., 2008). Even in prescription OD patients, those with a co-occurring psychiatric disorder had better opioid use outcomes after OAT than those without a co-occurring disorder, despite showing greater dependence and severity of substance abuse-related problems at baseline (Griffin et al., 2014). The possibility exists that in general, patients with OD are undertreated; however, when they have another comorbidity, they are cared for more carefully, which might explain why patients with dual pathology have better outcomes than patients with OD alone. This subject is controversial, as other studies have shown the opposite effects of psychiatric comorbidity on outcomes. Cacciola et al. (Cacciola et al., 2001) showed that having a previous psychiatric comorbidity was associated with poorer psychosocial and medical status at follow-up in OD patients undergoing methadone treatment.

Compton et al. (Compton et al., 2003) showed that men with psychiatric disorders in general and specifically men with major depression and those with antisocial personality disorder had worse treatment outcomes than men with no psychiatric comorbidities, although women seemed to show a smaller impact of psychiatric comorbidities on treatment outcome, and in the case of phobias, this effect was favourable on the outcome.

The results regarding patients receiving B/N should be cautiously interpreted because only 29 patients (4.7%) received this treatment. However, it is known that the dependence or independence of the psychiatric symptoms from the original SUD should be considered in treatment (Strain, 2002) and that depending on the type of psychiatric disorder, the use of a specific OAT may exert greater positive effects (Maremmani et al., 2011b; Schafer et al., 2010). The specificity and complexity of the dual OD patient should be taken into account when choosing the best opioid agonist for treatment. In agreement with a previous study reporting that higher dosages of methadone may be beneficial in decreasing Axis-I comorbidities (Herrero et al., 2011), our patients with at least one psychiatric comorbidity were being treated with larger doses of methadone. Higher doses of methadone have been previously used to stabilize patients with dual pathology compared to those with only opioid addiction (Eiden et al., 2012; Maremmani et al., 2000).

Some of the limitations of the study were already mentioned in a previous paper (Roncero et al., 2011). Instead of the initially planned 760 patients, only 631 were recruited, which could translate into some loss of precision in the statistical analyses. Second, the sample was heterogeneous, as most patients were poly-drug users. In addition, the diagnostic assessments were performed according to DSM criteria, but a structured interview was not used, and some bias could be introduced by the clinicians. Another limitation is that one has to be cautious when comparing the outcomes of patients on B/N OAT with the remaining population because only 4.7% of patients were being treated withB/N, while 93.6% received methadone. However, the psychiatric comorbidities were clinically diagnosed, and the study proportionally represented the whole of Spain according to autonomous communities, as the proportion of patients treated in each community to all the patients included in the Proteus study was similar

to the proportion treated in each community to the whole of Spain (PNSD, 2012).

It is interesting to note that theprevalence of mood and psychotic disorders resulted higher in the analysis of the patients' perceptions compared to the doctors' ones, showing an overestimation from the patients group. A previous study showed that OD patients were moderately reliable in their reports of trauma exposure, with personality disorder being one of the variables associated with variability in reporting (Mills et al., 2007). Therefore, OD patients seem to have a different perception of themselves and should always be assessed by a specialist, especially those claiming to present with a psychiatric comorbidity.

Because dual pathology is so frequent in patients receiving OAT in Spain, attending health care professionals should be aware and educated in the diagnosis and treatment of these psychiatric disorders. Despite the favourable outcomes of OAT in patients with dual pathology, and although the OD treatment alone might be sufficient to control psychiatric symptoms induced by SUDs, psychiatric disorders that are independent of substance use should be addressed specifically (Strain, 2002). In addition, OAT programmes might be improved by including psychiatric services, which has been shown to improve psychiatric outcomes when compared to off-site psychiatric care (Brooner et al., 2013).

4.1. Conclusions

In conclusion, the prevalence of psychiatric comorbidity in OD patients receiving OAT in Spain is very high (66.8%). In addition to mood, anxiety and personality disorders, the Spanish OD population shows a high rate of sleep disorders. Patients with dual diagnosis show more infectious and somatic comorbidities, worse working status and higher severity of all sorts of problems than patients without dual pathology. Despite these additional problems, 12% of patients with dual pathology are not being specifically treated. Patients with mood and anxiety disorders are especially complex because they have a greater use of other depressants and more frequent and severe legal and other issues compared with other OD patients. Because being male or female is associated with specific psychiatric disorders, a gender-based perspective should be incorporated regarding patients on OAT, especially with respect to those exhibiting mood disorders. The progression of dual diagnosis patients is controversial; some

studies support even better outcomes in dual diagnosis compared to non-dual diagnosis patients, which could be attributed to the adherence and effectiveness of OAT, even for other disorders.

Due to the high prevalence of dual pathology, the presence of psychiatric comorbidity should be assessed in all patients withOD. However, because our study reports a greater prevalence of comorbidity in OD patients receiving high methadone doses, special attention should be paid to patients requiring methadone at high doses. In the future, it is important to train professionals in the clinical detection and management of structured scales or interviews to improve the diagnosis process as well as the management of different treatments; additionally, it seems important to encourage enrolment in maintenance OAT in OD patients with dual disorders.

Conflict of interest

Carlos Roncero has received fees to give talks for Janssen-Cilag, Bristol-Myers Squibb, Ferrer-Brainfarma, Pfizer, Reckitt-Benckiser, Lundbeck, Otsuka, Servier, Lilly, Shire, GSK, Rovi and Adamed. Carmen Barral has received fees to give talks for Otsuka. Laia Rodríguez-Cintas has no conflicts of interest. Jesús Pérez-Pazos has received fees to give talks for Janssen. Nieves Martínez-Luna has received fees to give talks for Janssen-Cilag, Reckitt Benckiser and Otsuka. Miguel Casas has received fees to give talks for Janssen-Cilag, Bristol-Myers Squibb, Ferrer-Brainfarma, Pfizer, Reckitt-Benckiser, Lundbeck, Otsuka, Servier, Lilly, Shire, GSK, Rovi and Adamed. He has received financial compensation for his participation as a member of the Janssen-Cilag, Lilly, Shire, Lundbeck, Otsuka, Ferrer and Rovi board. Marta Torrens has received fees to give talks for Reckitt-Benckiser, Lundbeck and GSK. She has received financial compensation for her participation as a member of the Mundipharma, Reckitt-Benckiser and Lundbeck board. Lara Grau-López has received fees to give talks for Janssen-Cilag, Otsuka and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Figure 1. Mood and psychotic disorders according to patients (in the last month or lifelong) or doctors opinions

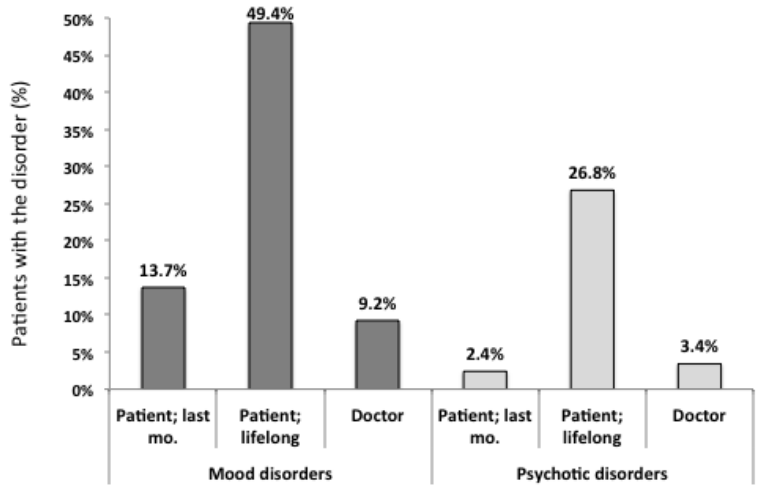

Table 1. Psychiatric comorbidities clinically diagnosed according to the DSM-IV-TR and distributed by sex

Variable	Men	Women	p-value[a]
Patients with at least one psychiatric comorbidity	351 (67.9%)	65 (66.3%)	0.7614
Infancy / childhood / adolescent disorders	24 (6.8%)	1 (1.5%)	NA
Delirium / dementia / amnesic disorders and other cognitive disorders	20 (5.7%)	0 (0%)	NA
Substance-related disorders	133 (37.9%)	18 (27.7%)	0.1162
Schizophrenia and other psychotic disorders	45 (12.8%)	2 (3.1%)	**0.0226**
Mood disorders	172 (49.0%)	30 (46.2%)	0.6729
Anxiety disorders	187 (53.3%)	35 (53.8%)	0.9326
Sexual and sexuality identity disorders	6 (1.7%)	4 (6.2%)	**0.0316**
Eating disorders	9 (2.6%)	3 (4.6%)	0.3641
Sleep disorders	146 (41.6%)	26 (40.0%)	0.8104
Impulse-control disorders not elsewhere classified	62 (17.7%)	7 (10.8%)	0.1698
Adjustment disorders	31 (8.8%)	1 (1.5%)	NA

Variable	Men	Women	p-value[a]
Personality disorders	95 (27.1%)	18 (27.7%)	0.9169
Other disorders that may be the focus of clinical attention	9 (2.6%)	1 (1.5%)	NA

[a] Chi-Squared test

Data expressed as n (%). In bold: significant p-values

*The result is statistically significant after Bonferroni correction
Somatoform, factitious and dissociative disorders and mental disorders due to medical conditions not elsewhere classified are not shown due to their very low representation (n≤7). NA (Not applicable): if any group was less than 2.

Table 2. Psychiatric comorbidities clinically diagnosed according to the DSM-IV-TR and distribution by methadone dose

Variable	<40	40-80	>80	p-value[a]
Patients with at least one psychiatric comorbidity	134 (60.9%)	159 (68.5%)	96 (77.4%)	**0.0066**
Infancy / childhood / adolescent disorders	8 (6.0%)	6 (3.8%)	7 (7.3%)	0.4535
Delirium / dementia / amnesic disorders and other cognitive disorders	4 (3.0%)	6 (3.8%)	8 (8.3%)	0.1307
Mental disorders due to medical conditions not elsewhere classified	1 (0.7%)	2 (1.3%)	4 (4.2%)	0.1256
Substance-related disorders	37 (27.6%)	57 (35.8%)	45 (46.9%)	**0.0109***
Schizophrenia and other psychotic disorders	18 (13.4%)	17 (10.7%)	10 (10.4%)	0.7050
Mood disorders	61 (45.5%)	87 (54.7%)	45 (46.9%)	0.2415
Anxiety disorders	71 (53.0%)	86 (54.1%)	54 (56.3%)	0.8857
Somatoform disorders	3 (2.2%)	1 (0.6%)	1 (1.0%)	0.4619
Factitious disorders	0 (0%)	0 (0%)	0 (0%)	-
Dissociative disorders	0 (0%)	1 (0.6%)	0 (0%)	0.4843
Sexual and sexual identity disorders	4 (3.0%)	4 (2.5%)	1 (1.0%)	0.6116
Eating disorders	2 (1.5%)	5 (3.1%)	3 (3.1%)	0.6223
Sleep disorders	56 (41.8%)	68 (42.8%)	40 (41.7%)	0.9797
Impulse-control disorders not elsewhere classified	26 (19.4%)	22 (13.8%)	19 (19.8%)	0.3379
Adjustment disorders	15 (11.2%)	9 (5.7%)	6 (6.3%)	0.1728
Personality disorders	29 (21.6%)	42 (26.4%)	30 (31.3%)	0.2574

Variable	<40	40-80	>80	p-value[a]
Other disorders that may be the focus of clinical attention	4 (3.0%)	3 (1.9%)	1 (1.0%)	0.5807

[a]Chi-Squared test

Data are expressed as n (%). In bold: significant p-values
*The result is statistically significant after Bonferroni correction

Table 3. Sociodemographic and clinical characteristics of patients with and without dual diagnosis.

	Dual (390)	Non-dual (194)	p-value
Age (yrs.)	39.0 ±6.7	37.4 ±7.3	**0.007**
Working status			**≤0.0001***
Unemployed	45.9	47.4	
Student	0.3	0	
Active	16.4	40.3	
Temporary disability	6.1	3.6	
Permanent disability	28	7.7	
Other	3.4	1	
Driving	45.3	65.5	**≤0.0001***
Infectious comorbidity	67.6	41.1	**≤0.0001***
Non-infectious comorbidity	49.3	20.8	**≤0.0001***
**Substance currently abused			
Heroin	35.3	38.5	0.555
Opioids	7.2	7.7	1
Cocaine	41.9	31.9	0.065
Benzodiazepines	52.4	15.4	**≤0.0001***
Cannabis	64.8	54.2	**0.046**
Alcohol	55.6	59.7	0.459
Tobacco	94.7	91.9	0.252
Severity of medical problem			**≤0.0001***
Absence	26.3	51.7	
Minimal	21	21.6	
Moderate	22.6	12.9	
Severe	20.6	12.1	
Extreme	9.5	1.7	
Severity of employment problem			**0.010**
Absence	23.9	37.1	
Minimal	16	21.6	
Moderate	18.1	17.2	
Severe	26.7	14.7	
Extreme	15.2	9.5	
Severity of alcohol problem			**≤0.0001***
Absence	51	73.3	

Minimal	20.2	16.4	
Moderate	14.4	7.8	
Severe	10.7	.9	
Extreme	3.7	1.7	
Severity of legal problem			**0.009***
Absence	62.1	76.7	
Minimal	16.9	9.5	
Moderate	9.5	5.2	
Severe	9.5	3.4	
Extreme	2.1	5.2	
Severity of family problem			**≤0.0001***
Absence	21.1	44	
Minimal	17.4	23.3	
Moderate	28.1	21.6	
Severe	22.3	5.2	
Extreme	11.2	6	
Severity of psychological problem			**≤0.0001***
Absence	12.3	46.6	
Minimal	16.5	29.3	
Moderate	29.2	20.7	
Severe	25.5	1.7	
Extreme	16.5	1.7	

Data are expressed as the mean ±SD for age and as patient percentages for all categorical variables. Only variables with significant statistically differences are shown.
*The result is statistically significant after Bonferroni correction
** The use of each specific drug was compared between the groups, and all of them are presented in the table (even those with no significant differences).

Table 4. Sociodemographic characteristics and substance use of patients with psychotic, mood, anxiety and sleep disorders compared to those without such disorders. Only variables with significant differences are shown.

	Psychotic disorders (45)	**All others (539)**	**p-value**
Sex: Men	95.8	83.2	0.021
Working status			
Unemployed	41.5	46.8	≤0.0001*
Student	0	0.2	
Active	4.9	26	
Temporary disability	2.47	5.4	
Permanent disability	51.2	18.7	
Other	0	2.8	
	Mood disorders (193)	**All others (391)**	**p-value**
Working status			
Unemployed	42.7	48.2	≤0.0001*
Student	0.5	0	
Active	15.7	28.7	
Temporary disability	7.6	4.1	

Permanent disability	30.3	2.3	
Other	3.2	11.3	
Driving	43.1	56.4	0.002*
Legal status			
No pending cases	74.4	82.3	
In prison	0	0.5	
Released on bail/parole	7.9	6.8	0.046
Other	17.7	10.4	
**Substance currently abused			
Benzodiazepines	54.3	35.2	≤0.0001*
	Anxiety disorders (213)	**All others (371)**	**p-value**
Age (yrs.)	37.9 ±7.1	39.6 ±6.4	0.003*
Working status			
Unemployed	44	47.8	
Student	0	0.3	
Active	14.8	30.1	
Temporary disability	7.7	3.8	≤0.0001*
Permanent disability	29.2	16.4	
Other	4.3	1.6	
Driving	44.8	56.1	0.007*
Current consumption	89.3	83.3	0.044
**Substance currently abused			
Cocaine	44.9	34.9	0.05
Benzodiazepines	59.6	30	≤0.0001*
	Sleep disorders (167)	**All others (417)**	**p-value**
Age (yrs.)	39.7 ±6.2	38.0 ±7.2	0.008*
Working status			
Unemployed	41	48.6	
Student	0.6	0	
Active	15.5	28	
Temporary disability	4.3	5.6	≤0.0001*
Permanent disability	34.2	15.9	
Other	4.3	1.9	
Driving	40.8	56.4	0.001*
**Substance currently abused			
Heroin	28.7	39.5	0.049
Benzodiazepines	59.8	34.7	≤0.0001*

Data are expressed as the mean ±SD for age and as patient percentages for all categorical variables

*The result is statistically significant after Bonferroni correction

**Categories: Heroin, Opioids, Cocaine, Benzodiazepines, Cannabis, Alcohol, Tobacco. Only drugs with significant differences are shown.

Highlights

- In total, 621 OD patients in Spanish OAT programmes were assessed for psychiatric comorbidities
- Psychiatric comorbidities were detected in 67% of patients
- Dual patients showed more infectious and non-infectious comorbidities than non-dual patients
- Dual patients showed worse working status and a higher severity of problems
- Dual patients were older and used benzodiazepines and cannabis more frequently