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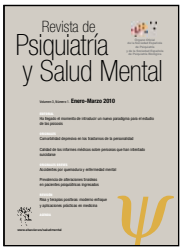

ORIGINAL ARTICLE

Psychiatric comorbidity in a sample of opiate-dependent patients treated with sublingual buprenorphine in a therapeutic community regime

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KEYWORDS
Buprenorphine;
Opiate dependency;
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Abstract
Introduction: The purpose of this work is to estimate the prevalence of psychiatric cases in a sample of opiate-dependent patients treated with sublingual buprenorphine in a therapeutic community regime, and to describe their progress during the first month of treatment.
Methods: An observational, longitudinal, prospective study was conducted. Of the 119 opiate-dependent patients selected, 46 agreed to start treatment with buprenorphine. For organisational reasons, the psychopathological assessment was carried out on 36 of these patients. The measurement tools used were the MINI, GHQ-28, IPDE and Assessment of the Quality of Life in Psychoactive Substance Addicts (TEQLASP).
Results: The prevalence rate of any psychiatric disorder was 78%. The prevalence of Axis I diagnoses was 69.4%. The prevalence of cases in Axis II was 58.3%, and 50% of patients had concomitant Axis I and Axis II disorders. The patients with Axis I psychiatric disorders showed a significant reduction in the mean scores of the GHQ-28 scale, and in the B (anxiety/unease), C (social dysfunction), and D (depression) subscales of the GHQ-28. The differences observed between the patients with no psychiatric disorders after one month of treatment were not significant. An improvement in the quality of life wad observed in both groups, although these changes were of a lower magnitude in the group with psychiatric disorders.
Discussion: The results of this study show a very high frequency of psychiatric disorders. For this reason, psychiatric illness must be actively looked for whenever we assess a drug-dependent patient.
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PALABRAS CLAVE
Buprenorfina;
Dependencia de opiáceos;
Trastorno psiquiátrico;
Comunidad terapéutica

Comorbilidad psiquiátrica en una muestra de pacientes con dependencia de opiáceos tratados con buprenorfina sublingual en régimen de comunidad terapéutica

Resumen
Introducción: El objetivo de este trabajo es estimar la prevalencia de casos psiquiátricos en una muestra de pacientes con dependencia de opiáceos tratados con buprenorfina sublingual en régimen de comunidad terapéutica y describir su evolución durante el primer mes de tratamiento.
Métodos: Estudio observacional, longitudinal prospectivo. Se seleccionó a 119 pacientes con dependencia a opiáceos, de los que 46 aceptaron iniciar tratamiento con buprenorfina. Por motivos organizacionales, la evaluación psicopatológica se realizó a 36 de estos pacientes. Los instrumentos de medida empleados fueron la MINI, el GHQ-28, el IPDE y el TECVASP.
Resultados: La prevalencia observada de cualquier trastorno psiquiátrico fue del 78%. La prevalencia de diagnósticos en el Eje I es del 69,4%. La prevalencia de casos en el Eje II es del 58,3%. Un 50% de los pacientes presentaban simultáneamente trastornos en el Eje I y en el Eje II. Los pacientes con trastornos psiquiátricos del Eje I presentan una reducción significativa en las puntuaciones medias de la escala GHQ-28, y en las subescalas B (ansiedad/angustia), C (disfunción social) y D (depresión) del GHQ-28. Entre los pacientes sin trastornos psiquiátricos en el Eje I, las diferencias observadas al mes del tratamiento no son significativas. En ambos grupos de pacientes se observa una mejora de la calidad de vida, si bien estos cambios son de menor magnitud en el grupo con trastornos psiquiátricos.
Discusión: Los resultados de este estudio señalan una frecuencia muy elevada de trastornos psiquiátricos. Por ello, se hace necesario explorar activamente la psicopatología siempre que evaluemos a un paciente drogodependiente.
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Introduction

Buprenorphine, widely used as an analgesic, is a semisynthetic opioid derived from thebaine. Jasinski[1] was the first to study its effectiveness in easing opioid withdrawal symptoms. Buprenorphine is a partial agonist at μ-opioid receptors and an antagonist at κ2-opioid receptors. Its efficacy as a drug for the treatment of opioid dependency has been extensively documented.[2] Although buprenorphine's efficacy indicators are similar to those of methadone, sublingual buprenorphine offers enhanced safety because of its so-called "ceiling effect." This means that, beyond a dosage of 24 mg/day, there is not a linear increase in the opioid effect or the potential for respiratory depression.[3] The introduction of buprenorphine into treatment programs, with methadone still in use, means that there can be an individualised approach for different patient profiles. This drug is marketed as 2 preparations for sublingual administration: Subutex® (buprenorphine in 2 mg and 8 mg tablets) and Suboxone® (buprenorphine/naloxone combination in a 4:1 ratio). While this drug has been prescribed for years in the majority of countries that surround us, here in our country, it is still in the implementation process.

The prevalence of psychiatric comorbidity in opioid-dependent patients is quite variable depending on the samplings studied and the instruments used, fluctuating between 47% and 93%, with depressive and anxiety disorders as well as borderline personality and antisocial disorders being the most common diagnoses.[4] Although a significant number of studies have focused on samplings of patients on methadone therapy,[5] there are still not very many studies that have explored the psychopathology of patients in buprenorphine treatment programs. Most studies have examined psychopathology as a predictive factor in the response to treatment more than they have estimated incidence.[6-8] There are no known studies published to date that estimate the incidence of psychiatric disorders in patients in buprenorphine treatment programs in an in-patient context.

The objective of this study was to estimate the incidence of psychiatric cases in a sampling of opioid-dependent patients on sublingual buprenorphine treatment in a therapeutic community and to describe their progress during the first month of treatment, assessed in terms of symptomatic relief and functional improvement (quality of life). The data analysed in this study was part of a wider study evaluating the efficacy of buprenorphine as supportive treatment in methadone withdrawal, the results of which may be consulted.[9,10]

Patients and methods

This was an observational (descriptive), longitudinal, prospective, and open (before-after design) study. A non-probability, sequential sampling procedure was used. The study protocol was approved by the *Comité Autonómico de Ensayos Clínicos de Andalucía (CAEC)* [Clinical Trial Committee for the Andalusian Autonomous Community],

and the study was conducted in accordance with the Declaration of Helsinki.

For each patient in the study, there was a maximum clinical observation period of 3 months. Because the majority of subjects complete the process of switching from one opioid to another in approximately 1 month, the first drug response assessment was done 4 weeks after the start of treatment, and the data was compared with the data obtained in the previous baseline assessment.

Patients were evaluated for comorbid psychiatric disorders through a clinical interview between day 30 and day 45 after their admission to the therapeutic community. This time frame was chosen to make the diagnosis of personality disorders (Axis II) more reliable and to rule out psychopathology symptoms that were more directly attributable to the intoxication or the withdrawal syndrome.

Buprenorphine treatment was offered to all patients admitted to the therapeutic community whose methadone dosage was not more than 80 mg/ day and who, upon clinical assessment, appeared to be candidates for beginning a gradual withdrawal from this drug during their admission. Of the total number of patients selected (119), 46 consented to starting buprenorphine treatment, but the psychopathology assessment was possible in only 36 of them for reasons of an organisational nature. The remaining 73 patients decided to continue with methadone treatment. The procedures we used in this study for tapering the methadone dosage and for buprenorphine induction may be found in other studies already published.[9,10]

The inclusion criteria were as follows: 1) diagnosis of "opioid dependence on agonist treatment" per DSM-IV-TR criteria and currently in a methadone treatment program at the referring Centre; 2) taking a maximum dose of 40 mg/ day of methadone for 1 week prior to buprenorphine induction; 3) patient who was about to begin or was currently in the "withdrawal phase" of the methadone treatment program, as determined by clinical impression; and 4) signing the informed consent. The exclusion criteria were: 1) subjects with pending legal charges who were expecting to begin serving their sentence within the next 6 months; 2) women who were pregnant or breastfeeding; and 3) methadone dosage of more than 80 mg/ day.

The contrast statistic used for comparing the baseline assessment with the assessment after 1 month of treatment was the non-parametric Wilcoxon test, given the reduced size of the groups (with and without psychiatric disorders). Effect size was calculated using Cohen's d statistic.[11]

Measuring instruments

For assessing the major DSM-IV-TR Axis I diagnoses, we used the Mini International Neuropsychiatric Interview (MINI).[12] It has been validated for our setting[13,14] and shown to be useful in diagnosing psychiatric comorbidity in opioid-dependent patients.[15] As a global measure of the "severity" of "general psychopathology," we used the total score on the General Health Questionnaire (GHQ-28).[16,17]

To identify personality disorders (Axis II), we used the full version of the International Personality Disorder Examination (IPDE).[18] In this study, it was used following the DSM-IV-TR criteria.

The *Test para la Evaluación de la Calidad de Vida en Adictos a Sustancias Psicoactivas* (TECVASP)[19] [Test for Quality of Life Assessment in Psychoactive Substance Addicts] is a self-administered scale consisting of 22 items that assess elements of physical, psychological, and social health. Its objective is to determine how the substance addiction impacts the individual's daily living. This is a quality of life instrument specific for the drug-dependent population, and it is based on the Edwards and Gross bi-axial concept of addiction.[20] Low scores on this scale correspond to poor quality of life and high scores to a high quality of life.

Results

The 36 patients who began buprenorphine treatment and were assessed were males whose mean age was 37.6 years (dt=7.1). Of the sampling subjects, 68.4% had only a primary level of education; 65.2% were unemployed; 48.9% had a legal history; and 52.8% reported having used opioids during the month prior to admission, with 15.8 years (dt=5.8) being the mean length of time they had been using. With regard to other abused substances used during the previous month, 63.9% had used alcohol and cocaine, and 55.6% had used cannabis. Prior to the start of treatment, in the sampling of patients who started buprenorphine induction, the mean GHQ-28 score was lower than that of the subjects who decided to continue on methadone (9.7 and 12.7, respectively), this being a statistically significant difference.

The observed incidence of psychiatric disorders as a whole was 78% (cases where the patient presented with at least 1 Axis I or Axis II diagnosis, not including the substance use disorders). Table 1 shows the relative frequencies for each of the Axis I and Axis II disorders. The observed incidence of Axis I diagnoses was 69.4%, the most common being the affective and anxiety disorders, with a surprising number of cases of suicide risk and previous manic episodes. The incidence of Axis II cases was 58.3%, borderline and antisocial disorders being the most common. The presence of mixed ("non-specific") personality disorders was noteworthy. Simultaneous Axis I and Axis II disorders were seen in 50% of the patients.

As shown in table 2, patients with Axis I psychiatric disorders had a statistically significant reduction in the mean total GHQ-28 score. A significant reduction was also noted in the scores on GHQ-28 subscales B (anxiety/ stress), C (social dysfunction), and D (depression). In all these cases, the Cohen's d statistic, which estimates effect size, took values greater than 0.8 ("large"). The depression subscale is a noteworthy case, where a reduction of more than 62% was observed. Among patients who had no Axis I psychiatric disorder (table 3), the differences observed after 1 month of treatment were slight and not statistically significant.

Tables 2 and 3 also show that in both the group that had and the group that did not have an Axis I disorder, scores on the quality of life scale increased, even though

Table 1 Frequency distribution for axis I and axis II psychiatric disorders (n=36)

Diagnosis	No.	Percentage	95% CI
Axis I Psychiatric Disorders			
Current major depressive D.	0		
Recurrent major depressive D.	0		
Major depressive D. with melancholic features	0		
Mood D. with psychotic features	0		
Current dysthymic D.	10	27.8%	12.4%-43.1%
Suicide risk (mild+high)	11	30.6%	10.1%-39.9%
Current manic episode	0		
Past manic episode	8	22.2%	7.9%-36.5%
Current hypomanic episode	0		
Current stress D.	2	5.6%	−2.3%-13.4%
Generalised anxiety D.	13	36.1%	19.6%-52.6%
Agoraphobia	8	22.2%	7.9%-36.5%
Social phobia	3	8.3%	−1.1%-17.8%
Obsessive-compulsive D.	0		
Post-traumatic stress D.	1	2.8%	−2.8%-8.4%
Previous psychotic D.	1	2.8%	−2.8%-8.4%
Current psychotic D.	1	2.8%	−2.8%-8.4%
Restricting-type anorexia nervosa	0		
Purging-type anorexia nervosa	0		
Bulimia nervosa	1	2.8%	−2.8%-8.4%
Total patients with Axis I psychiatric disorders	25	69.4%	53.6%-85.3%
Axis II psychiatric disorders			
Paranoid D.	1	2.8%	−2.8%-8.4%
Schizoid D.	0		
Schizotypal D.	0		
Antisocial D.	11	30.5%	10.1%-39.9%
Borderline D.	6	16.7%	2.9%-23.1%
Histrionic D.	1	2.8%	−2.8%-8.4%
Narcissistic D.	0		
Evasive D.	5	13.9%	1.5%-20.2%
Obsessive-compulsive personality D.	1	2.8%	−2.8%-8.4%
Mixed personality D.	9	25%	10.1%-39.9%
Total patients with Axis II psychiatric disorders	21	58.3%	41.4%-72.3%
Total patients with Axis I or II psychiatric disorders	28	78%	63.5%-92.0%

Table 2 Progression in measurements of the severity of psychopathology symptoms and quality of life for patients with axis I disorders (n=25)

	Group with Axis I disorder					
	Baseline (dt)	1 month (dt)	Diff. means	95% CI	Z	Cohen's d
GHQ-28 Scale	9.96 (9.2)	2.92 (4)	7.04 (9.6)	11.00-3.67	−3.074*	0.992
Subscale A (somatic symptoms)	2.16 (2.6)	1.24 (1.9)	0.92 (2.8)	−0.27-2.11	−1.074	0.404
Subscale B (anxiety/stress)	2.8 (2.6)	1 (1.6)	1.8 (2.7)	0.68-2.92	−2.785*	0.833
Subscale C (social dysfunction)	2.52 (2.8)	0.36 (0.9)	2.16 (2.9)	0.96-3.36	−3.029*	1.039
Subscale D (depression)	2.48 (2.9)	0.32 (0.6)	2.16 (2.9)	0.95-3.37	−3.029*	1.032
TECVASP Scale (quality of life)	0.51 (0.7)	0.8 (0.6)	−0.29 (0.8)	−0.68-0.04	−1.749	0.460

Effect size interpretation categories for Cohen's d values: 0.2-0.5 small; 0.6-0.8 medium; above 0.8 large.
* $P<.01$.

Table 3 Progression in measurements of the severity of psychopathology symptoms and quality of life for patients without axis I disorder (n=11)

	Group with Axis I disorder					
	Baseline (dt)	1 month (dt)	Diff. means	95% CI	Z	Cohen's d
GHQ-28 Scale	2.82 (3.3)	3.91 (4.4)	−1.09 (4.5)	−4.11-1.94	−0.985	0.280
Subscale A (somatic symptoms)	1.1 (1.6)	1 (1.6)	−0.09 (2.2)	−1.36-1.55	−0.073	0.063
Subscale B (anxiety/stress)	0.73 (1.5)	1.64 (2.3)	−0.91 (1.8)	−2.13-0.31	−1.549	0.469
Subscale C (social dysfunction)	0.55 (1.2)	1.1 (1.3)	−0.55 (1.6)	−1.64-0.55	−0.828	0.439
Subscale D (depression)	0.45 (1.2)	0.18 (0.4)	0.27 (1.3)	−0.63-1.18	−0.378	0.302
TECVASP Scale (quality of life)	0.82 (0.6)	1.3 (0.7)	−0.48 (0.5)	−0.79 - −0.15	−2.446*	0.767

*$P<.05$. Effect size interpretation categories for Cohen's d values: 0.2-0.5 small; 0.6-0.8 medium; above 0.8 large.

these changes were of lesser magnitude in the group that did have psychiatric disorders and their mean values after 1 month of treatment were indicative of a poor state.

Discussion

The results of this study indicate a rather high incidence of psychiatric disorders, consistent with data in the literature[6,21,22] for patients being treated with agonists. The scant incidence of psychotic disorders among cases with an Axis I diagnosis is remarkable, especially in view of the fact that substance use is high among patients with schizophrenia.[23] One possible explanation for this finding is that, in Andalusia, the public healthcare system for drug addicts and the mental health care system are administratively separate, which means that patients with comorbidity (dual pathology) who are seen in both systems may have a different profile in each one. Among the Axis II diagnoses, the higher incidence of borderline and antisocial disorders is also consistent with data in the literature,[24] and these are a crucial factor in a poor prognosis.

At 1 month following initiation of the treatment, patients with Axis I disorders experienced a more obvious improvement in the severity of their psychopathology symptoms than did patients without an associated psychiatric disorder. Given that baseline values were less favourable in the group with comorbidity, as is logical, we believe that this change could be due partly to a genuine clinical improvement and partly to a phenomenon of regression to the mean, which we cannot rule out because this was an open and uncontrolled study. We were surprised by the magnitude of the improvement on the depressive symptoms scale, although this data is consistent with that seen by Gerra et al[6] in other samplings of patients on buprenorphine treatment. These authors attribute this observation to the potential for buprenorphine to have an antidepressant effect by virtue of its κ-opioid receptor antagonism. On the other hand, it should be pointed out that the lack of significant differences on the GHQ for the group of patients without Axis I disorders was to be expected, given that their baseline scores were very low.

Of the 119 patients selected for our study who were offered a choice between continuing on methadone or starting buprenorphine treatment, 38.6% opted for the latter drug. The group of patients who decided to switch to buprenorphine had less severe psychopathology on the baseline assessment than those who decided to continue with methadone treatment. Oddly enough, in a recent study where patients were also given this opportunity to choose, it was likewise 37% of the sampling who opted for buprenorphine treatment, and their psychopathology was less severe than in the group that opted for methadone.[25] In another study, Ridge et al[26] indicated that this preference for methadone over buprenorphine could be related to a previous positive experience with this drug which, in turn, would mean it was more likely to be prescribed by their doctor. It is difficult to come up with a simple explanation for this finding in terms of a differential psychopathology profile, especially in light of the most recent studies indicating comparable efficacy[27] and similar retention and results[28] predictors for these 2 types of treatment. In any case, we believe a possible confusion factor would have to be explored stemming from the fact that patients on high-dose methadone treatment, who initially could not be switched to buprenorphine, have more psychopathology symptoms (especially anxiety, depression, and impulsivity features).

We have also observed that, compared to patients who have only an opioid dependence, patients with comorbid psychiatric disorders have a lower quality of life and also see less improvement in that with treatment. This finding is also consistent with studies that establish a worse prognosis for patients with dual pathology.[29]

One of the limitations of this study was the small sample size, but this approach appealed to us because none of the very few studies on buprenorphine treatment published to date in our country involved a psychopathology assessment. Another limitation of the study stems from the instrument used to evaluate the presence of Axis I disorders. Although the MINI has been used previously in samplings of opioid-dependent patients,[13] it is an instrument that has serious limitations when it comes to differentiating between substance-induced disorders and primary or non-induced

disorders—a differentiation that can be made using interviews such as the Psychiatric Research Interview for Substance and Mental Disorders (PRISM).[30,31]

In view of the high incidence of psychiatric comorbidity seen in this study and reported in various reviews, whenever we are evaluating a drug-dependent patient, it is essential that his/her psychopathology be actively explored, using the appropriate instruments.

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Conflict of interest

The authors declare no conflict of interest.

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