

Joaquín C. Martín<sup>1</sup>  
María J. Acuña<sup>1</sup>  
José Labrador<sup>1</sup>  
Matilde Blanco<sup>1</sup>  
Cristina Casas<sup>1</sup>

# Sexual dysfunction factors in patients with schizophrenia treated with second generation antipsychotics: not only prolactin

<sup>1</sup> Unidad de Gestión Clínica de Salud Mental. Hospital Universitario de Valme. Sevilla. España

**Introduction.** Despite the high prevalence of sexual dysfunction in patients with schizophrenia, its origins are still unclear. The aim of this study: to determine the prevalence and causal factors of sexual dysfunction in a group of outpatients with schizophrenia.

**Methods.** The study was designed to be cross-sectional and naturalistic, including outpatients with schizophrenia undergoing second generation antipsychotic monotherapy. Patients receiving antidepressants and/or mood stabilisers were excluded.

The following data were recorded: sexual functionality, sociodemographic information, sexual history, psychotic and depressive psychopathology, metabolic syndrome and BMI.

Psychotropic-Related Sexual Dysfunction Questionnaire (PR SexDQ-Salsex); Positive and Negative Syndrome Scale; Hamilton Depression Rating Scale; Plasma concentrations of prolactin, testosterone, estradiol, progesterone and the International Diabetes Federation diagnostic criteria for metabolic syndrome, were used to complete the study.

**Results.** Of the 57 patients included in the study, 80% exhibited sexual dysfunction, one-third of which suffered severe levels of dysfunction. However, only 30% of patients spontaneously reported this problem. Although there were significant differences in the prevalence of hyperprolactinemia and metabolic syndrome according to the antipsychotic received, multivariate regression analysis did not show a correlation between sexual dysfunction and prolactin, sexual hormones, type of antipsychotic received, psychotic psychopathology or metabolic syndrome. Sexual dysfunction was only associated with age, civil status and depressive psychopathology.

**Conclusions.** There is a high prevalence of sexual dysfunction in the patients with schizophrenia who participated in the study, but it was only associated with higher age,

being single or divorced or having depressive psychopathology; this suggests a multifactorial etiology for sexual dysfunction in schizophrenia.

**Key Words:** Schizophrenia, Sexual Dysfunction, Antipsychotics, Psychopathology, Prolactin

*Actas Esp Psiquiatr 2018;46(6):217-25*

## Factores de disfunción sexual en pacientes con esquizofrenia tratados con antipsicóticos de segunda generación: no solo prolactina

**Introducción.** Pese a la alta prevalencia de disfunción sexual en pacientes con esquizofrenia, su origen es todavía incierto. Propósito de este estudio: determinar la prevalencia y factores causales de la disfunción sexual en un grupo de pacientes con esquizofrenia ambulatorios.

**Metodología.** El diseño del estudio es transversal, naturalístico, incluyendo pacientes con esquizofrenia ambulatorios, en monoterapia con antipsicóticos de segunda generación. Los pacientes en tratamiento con antidepresivos y/o estabilizadores del ánimo fueron excluidos. Se registró función sexual y datos sociodemográficos, historia sexual, psicopatología psicótica y depresiva, síndrome metabólico e IMC.

Se utilizó para el estudio: Escala para la medida de la Disfunción Sexual Secundaria a los Psicofármacos (PRSex DQ-Salsex); Escala del Síndrome Positivo y Negativo; Escala de Evaluación de la Depresión de Hamilton; concentraciones plasmáticas de prolactina, testosterona, estradiol y progesterona y los criterios de Síndrome Metabólico de la Federación Internacional de Diabetes.

**Resultados.** De los 57 pacientes incluidos en el estudio, 80% presentaban disfunción sexual, un tercio en grado intenso. Pero solo un 30% de pacientes comunicó espontáneamente este problema. Aunque existían diferencias significativas en la prevalencia de hiperprolactinemia y síndrome metabólico según el antipsicótico recibido, el análisis de

Correspondence:

Joaquín C. Martín

E-mail: joaquinmartinm@hotmail.com

regresión multivariante no reveló relación de la disfunción sexual con prolactina, hormonas sexuales, tipo de antipsicótico recibido, psicopatología psicótica ni síndrome metabólico. La disfunción sexual solo se asoció con la edad, con estar soltero o divorciado y con la psicopatología depresiva.

**Conclusiones.** Existe una alta prevalencia de disfunción sexual en los pacientes con esquizofrenia del estudio, pero solo se asocia con mayor edad, estar soltero o divorciado y tener sintomatología depresiva, sugiriendo una etiología multifactorial de la disfunción sexual en la esquizofrenia.

**Palabras Clave:** Esquizofrenia, Disfunción Sexual, Antipsicóticos, Psicopatología, Prolactina

## INTRODUCTION

Numerous studies confirm the existence of sexual dysfunction in patients suffering from Schizophrenia<sup>1-3</sup>; present in patients in remission<sup>4</sup> and outpatients<sup>5</sup>, as well as patients with severe symptomatology of the disorder<sup>6</sup> or who have been institutionalised<sup>7</sup>. Sexual dysfunction is reported at higher rates than in the general population<sup>8</sup>. According to a recent investigation into the subject<sup>9</sup>, carried out by means of self-administered questionnaires show a range of 16-60%. Regrettably, there are a limited number of studies dealing with the topic of sexual dysfunction in schizophrenia<sup>10</sup>.

Sexual dysfunction has a great impact on the patient's quality of life<sup>11,12</sup>, given that their interest in sexuality does not differ from that of healthy individuals<sup>9</sup>. This is true even of patients who have spent years residing in institutions<sup>7</sup>. Patients with schizophrenia indicate that the principal motivation for their sexual activity is the pursuit of love and affection<sup>13</sup>. Regardless, a patient's sexual dysfunction is rarely addressed by their psychiatrist. The frequency of questions related to the patient's sexuality<sup>14</sup> is quite low, at only 25%. Further complicating matters, according to some studies<sup>1</sup> less than 38% of patients spontaneously report any sexual dysfunction.

Sexual dysfunction is one of the primary causes of non-compliance in antipsychotic treatments. Some studies indicate that up to 41% of men and 15% of women had stopped taking their medications for this reason<sup>6</sup>.

Hyperprolactinemia, caused by the D<sub>2</sub> antagonist effect of the majority of traditional antipsychotics, is considered one of the main causes of sexual dysfunction in schizophrenia<sup>8</sup>. However, even the newest second generation antipsychotics, having different D<sub>2</sub> antagonist effects, are also asso-

ciated with sexual dysfunction<sup>2,15</sup>. Nevertheless, recent research demonstrates a reduction in hyperprolactinemia and sexual dysfunction with second generation antipsychotics like Quetiapine and especially Aripiprazol<sup>9,16,17</sup>. Sexual dysfunction related to hyperprolactinemia could be due not only to its hypogonadal effects, but also a direct effect of the prolactin in the dopaminergic system<sup>18</sup>. This association with sexual dysfunction could even be due to genetic polymorphism in D<sub>2</sub> receptors<sup>19</sup>. However, hyperprolactinemia may not be a by-product of antipsychotics, since different studies indicate high levels of prolactin even in antipsychotic treatment-naïve patients<sup>20-22</sup>. Furthermore, antipsychotics may cause sexual dysfunction by reducing penile blood flow due to peripheral blockage of  $\alpha$ -adrenergic receptors, and the sedative qualities that some of them demonstrate, decreasing sexual activity<sup>10</sup>.

Other possible factors should be considered as well. There is a high prevalence of metabolic syndrome (estimated from 28.8% to 44.6%) in patients with schizophrenia<sup>23</sup>, and recent investigations show that amongst the general population, erectile dysfunction is almost tripled (a 2.6 fold increase) in persons with metabolic syndrome<sup>24</sup>. Another possible cause could be schizophrenic pathology itself, with sexual dysfunction correlating to a heightened severity of positive and negative symptomatology<sup>9</sup>. Paradoxically one study<sup>4</sup>, using a sample of patients in remission, found that severe positive psychopathology protects against sexual dysfunction. A limited number of studies have investigated a possible link to depressive psychopathology, finding either no relation<sup>25</sup> or attributing its cause to clinical depression<sup>26</sup>.

Further complicating the matter, sexual dysfunction has been observed in persons with an ultra high risk of psychosis even before being diagnosed with schizophrenia<sup>26</sup>. Research done on sexual dysfunction in schizophrenia frequently includes complicating factors like the ancillary use of antidepressants and/or mood stabilisers, medications with a recognised affect on sexual functioning<sup>27,28</sup>.

The inconsistency of these findings suggests that at the moment, the etiopathogeny of sexual dysfunction demonstrated by patients with schizophrenia is far from clear and that it could be associated with various other factors.

The objective of this study was to determine the prevalence of sexual dysfunction in outpatients of both sexes with schizophrenia treated with second generation antipsychotic monotherapy, but without antidepressants or mood stabilisers.

The specific objective was to verify the hypothesis that sexual dysfunction in patients with schizophrenia is associated with various factors: sociodemographic profiles of the patients, antipsychotics received, psychotic and depressive psychopathology, prolactin and other sexual hormones, metabolic syndrome and Body Mass Index (BMI).

## METHODS

The study was designed to be cross-sectional and naturalistic, with all procedures completed in only two days. It was carried out in four Public Mental Health Centres in the province of Seville (Spain) between 2012 and 2015. All seven participating researchers were the referring psychiatrists of the patients included in the sample. Patients were not selected randomly, per the observational structure of the study.

The criteria for inclusion in the sample were: 1) Outpatients of both sexes, diagnosed with schizophrenia or schizoaffective disorder, according to the standards established by the 10<sup>th</sup> International Classification of Diseases<sup>29</sup>, the official classification used in our region. Patients with any degree of severity of schizophrenic disorder were admitted, as long as it did not impede the correct implementation of the study. 2) Second generation antipsychotic monotherapy with a duration of more than six months. 3) Patients of 18 to 65 years of age.

The criteria for exclusion were: 1) Severe somatic pathology and/or somatic medication that could affect sexuality. 2) Cognitive impairment. 3) Patients who had taken antidepressants and/or mood stabilisers in the six months prior to their inclusion in the study. 4) Treatment noncompliance. 5) Women who were nursing or pregnant.

Concurrent treatments using anxiolytics were permitted due to the negligible effects on sexuality they produce<sup>28</sup>.

## Assessments

The demographic characteristics, psychiatric antecedents, medication and sexual history of the patients were recorded (Table 1). Sexual functionality was evaluated using the Psychotropic Related Sexual Dysfunction Questionnaire (PRSexDQ-Salsex). It is an easy to use, non self-administered questionnaire. Drafted in Spanish, it is the only non self-administered questionnaire approved for patients with schizophrenia<sup>30</sup>. It is composed of seven items. The first item evaluates the presence of any kind of sexual alteration; the second evaluates the spontaneous communication of sexual dysfunction by the patient. Items 3-6 evaluate the four dimensions of sexual function: decreased libido, delayed orgasm or ejaculation, erectile dysfunction or decreased vaginal lubrication. Points are awarded on the basis of severity or frequency using a scale of 0 to 3, where 0=none and 3=severe. Item 7 evaluates the patient's tolerance to sexual dysfunction, with 0=no sexual dysfunction and 3=poor tolerance. Sexual dysfunction is defined as having a score greater than or equal to 1 in any of the four dimensions of items 3-6 of the Salsex. The final score is the summation of items 3-7, with an additional qualitative score: mild sexual dysfunction (1-5 total points, with no item  $\geq$  2), moderate

(6-10 points, or with any item=2 and  $<$  3) and intense (11-15 points or with any item=3).

Schizophrenic pathology was evaluated using a certified Spanish translation<sup>32</sup> of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)<sup>31</sup>. Given the complexity of this scale, all researchers were trained in its use beforehand according to the standardised training guidelines<sup>33</sup>. Symptoms of depression were assessed using the Hamilton Depression Rating Scale (HADRS)<sup>34</sup>. The use of this scale is widespread and it continues to be the most commonly used for evaluating depression in schizophrenia<sup>35</sup>.

Plasma levels of prolactin and of the sexual hormones testosterone, estradiol and progesterone were extracted, and after fifteen minutes a second sample of prolactin was obtained through the same cannula. This was done to reduce the stress caused by blood extraction, which can cause an increase in prolactinemia<sup>21</sup>. Factors associated with metabolic syndrome were also evaluated, according to the criteria established by the International Diabetes Federation<sup>36</sup> and the Body Mass Index.

## Statistical Analysis

Descriptive statistics of all the variables of the analysis were derived implementing measures of central tendency and dispersion for quantitative variables, as well as absolute and relative frequencies for qualitative variables, with a 95% confidence interval in both cases.

The distribution type of the variables and its adjustment to the Gauss distribution (using the Kolmogorov-Smirnov test) was studied. The statistical significance of the comparison between groups was calculated using nonparametric tests, since in the majority of the subgroups the total was less than 30. 2x2 table comparative analysis between the groups (independent samples) was done using the Mann-Whitney U test for continuous variables, Fisher's exact test for binary qualitative variables, the Mantel-Haenszel test for ordinal variables and the association between two continuous variables was tested using Spearman's correlation coefficient.

Linear regression analysis was done to test the hypothesis that sexual functionality is not only hormonal, but also related to other factors; using the total score from the Salsex as a dependent variable and with sexual hormones, psychotic symptoms, symptoms of depression, sociodemographic data, metabolic syndrome and BMI as independent variables. An initial univariate analysis was carried out, followed by a multivariate analysis for the independent variables which proved to be significant.

No adjustments were made to control type I errors for multiplicity. Statistical trials were bilateral and were carried out with a significance level of 5%. All analysis was done using SAS statistical analysis software version 9.4.

Table 1		Sexual History, Clinical and Demographic Data			
Variable	N	Mean	SD	Percentage	
Age (years)	57	41.5	10.9		
Male	42	41.1	11.5	73.7	
Female <sup>1</sup>	15	42.6	9.3	26.3	
<b>Education Level</b>					
Reading/Writing	4			7	
Primary Studies	32			56.1	
Secondary Studies	16			28.1	
Higher Education	5			8.8	
<b>Civil Status</b>					
Single	39			68.4	
Divorced	7			12.3	
Married/With a Partner	11			19.3	
<b>Living Arrangements</b>					
Alone	6			10.5	
Own Family	11			19.3	
Family of Origin	40			70.2	
<b>Employment Status</b>					
Pensioner	41			71.9	
Unemployed	12			21.1	
Employed	4			7	
Duration of Schizophrenia(years)		15	9.8		
Number of Psychiatric Hospitalizations	142	2.6	4.4		
Initiation of Sexual Activity (Age)		19.4	4.9		
<b>Current Sexual Activity</b>					
No	14			24.6	
Yes	43			75.4	
<b>Current Sexual Partner</b>					
No	41			71.9	
Yes	16			28.1	

<sup>1</sup>There were no significant differences of age between men and women (p= 0.57, Mann-Whitney U Test)

## Ethical Considerations

All patients gave written informed consent and received a printed copy. The study was approved by the relevant Ethics Committee and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice.

## RESULTS

A total of 57 outpatients with schizophrenia participated in the study; 42 men and 15 women. 20 patients who met all of the criteria and were asked to take part in the study

chose not to participate, with an unwillingness to discuss their sexuality being the most frequent reason given.

Table 1 shows the sociodemographic and clinical characteristics of the patients involved in the study. The men and women were of similar ages. The sample contained a wide range of ages from 20 to 62 years of age, with the 25<sup>th</sup> percentile aged 34, the 50<sup>th</sup> aged 41, and the 75<sup>th</sup> aged 50. The sociodemographic data indicates that the majority were single (68%), living with their families (70%) with a basic/primary level of education (63%) and as pensioners (72%). The clinical data (table 1) shows a long development of the illness (mean=15 years), but with a moderate number of psychiatric

hospitalisations (mean=2.6). The patients' sexual history (Table 1) shows a late initiation of heteroerotic relations at 19 years of age, and notably 17% of the patients reported having only an autoerotic sexuality. Although 71.9% of patients did not currently have a sexual partner, 75.4% reported having maintained some type of sexual activity.

Psychiatric medications are specified in table 2, with the plasma levels of prolactin in table 3. Levels of prolactinemia are displayed according to each antipsychotic. Due to the reduced size of the sample and given the similar neurobiochemical and clinical profile of risperidone and paliperidone<sup>37</sup>, their values have been grouped together. Additionally the separate entry for quetiapine has been removed (Table 3). Levels of prolactinemia after fifteen minutes (mean=19.1, SD 15.8) diminished 0.9 points with respect to their base levels (mean=20, SD 16.1), and in some antipsychotics this was a significant reduction. There were also significant differences between basal levels of prolactinemia and levels after 15 minutes between the different antipsychotics, with aripiprazol being lower than the normal range (mean=3.98) and with risperidone/paliperidone indicating hyperprolactinemia (mean=30). There were no appreciable differences observed between the different antipsychotics in the remaining sexual hormones, with their average values within the normal range: estradiol 48.2 pg/ml (DS 74.8); testosterone 3.6 ng/ml (DS 2.5) and progesterone 0.93 mg/ml (DS 0.7).

There were significant differences between the various antipsychotics in the prevalence of metabolic syndrome, but

none with respect to the BMI. Not one of the patients treated with aripiprazol had complete metabolic syndrome (p=0.02, Fisher's exact test).

The ratings of sexual dysfunction evaluated by the Salsex are shown in table 4, indicating no differences according to the antipsychotic treatment received. 80.7% of patients exhibited some degree of sexual dysfunction, which in 33% reached intense levels. Regardless, only 29.8% of patients spontaneously reported sexual dysfunction (Table 4). The PANSS and HADRS results (Table 5) show a moderate degree of psychopathology, though there were 19 patients with a HADRS score of >7 points, (which indicates mild depression) and with a total average Salsex score of 6 (SD 3.14), significantly higher than the sample's average of 4.26. No association between depression and the antipsychotic treatment received was found.

The association between sexual dysfunction and the different variables analysed using multivariate linear regression, shows that only age, civil status and HADRS score correlate significantly to sexual dysfunction (Table 6). The remaining sociodemographic data, the antipsychotic received, prolactin (and the three other hormones studied), metabolic syndrome, Body Mass Index and schizophrenic pathology were not associated with sexual dysfunction.

## DISCUSSION

In our sample, 80% of patients with schizophrenia suffered from some degree of sexual dysfunction, a proportion

Table 2	Psychopharmacological Treatment		
	Frequency	Percentage	Mean Dose (SD)
<b>Antipsychotics</b>			
Aripiprazole	9	15.7	14.4 (6.3)
Clozapine	7	12.2	400 (152.7)
Olanzapine	18	31.6	15.2 (6.9)
Depot Paliperidone	8	14	87.5 (46.3) <sup>1</sup>
Oral Paliperidone	4	7	11.2 (5.1)
Quetiapine extended-release	1	1.7	500
Depot Risperidone	4	7	34.5 (12) <sup>2</sup>
Oral Risperidone	6	10.5	5.5 (2.2)
<b>Others</b>			
Benzodiazepines	23	40.3	
<sup>1</sup> Dosage every 30 days			
<sup>2</sup> Dosage every 15 days			

Table 3	Plasma levels of Prolactin by Antipsychotic Drug			
	Aripiprazol	Clozapine	Olanzapina	Risperidone/ Paliperidone
<b>Prolactinemia</b>				
N	8	7	17	22
Mean (SD)	4.2(3.3)	13 (7)	15.7(10.8)	31.4(17.1)
C.I. 95%	(1.4; 7)	(6.5; 19.4)	(10.2; 21.3)	(23.8; 39)
Median (P25/P75) <sup>a</sup>	3.3 (2.5/4.8)	11.9 (6.2/15.2)	12.9 (6.9/19.4)	27.7 (18.8/44.3)
<b>Prolactinemia at 15 minutes</b>				
N	7	6	17	22
Mean (SD)	4(3.5)	14.4(7.1)	13.1(9.3)	30 (17.2)
C.I. 95%	(0.7; 7.2)	(7; 21.8)	(8.3; 17.9)	(22.4; 37.7)
Median (P25/P75) <sup>a</sup>	3.3 (1.9/4.3)	14.1 (8.7/18.9)	9.8 (5.9/16.6)	26.1 (16.4/44.1)
<b>Change in prolactinemia at 15 minutes</b>				
N	7	6	17	22
Mean (SD)	-0.1(0.3)	0.1 (3.5)	-2.6 (2)	-1.4 (2)
C.I. 95%	(-0.4; 0.2)	(-3.5; 3.8)	(-3.7; -1.6)	(-2.3; -0.5)
Median (P25/P75) <sup>b</sup>	-0.2 (-0.2/0)	-0.9 (-1.7/-0.2)	-1.6 (-3.7/-1)	-1.5 (-2.5/-0.2)

<sup>a</sup> p value < 0.0001. Kruskal-Wallis test  
<sup>b</sup> p value =0.0023. Kruskal-Wallis test

similar to other studies that have reported 80%<sup>10</sup>, and even up to 88%<sup>4</sup>. Although a third of the patients exhibited severe dysfunction that always or nearly always affected one of the 4 dimensions of sexuality that we explored, only 30% spontaneously reported having this problem. This lines up with other studies<sup>1</sup> underscoring the need for a specific approach to this issue by healthcare professionals.

Similarly to other studies<sup>38,39</sup>, hyperprolactinemia was not associated with sexual dysfunction. Nevertheless, our study did indicate significant differences in levels of hyperprolactinemia according to the antipsychotic received, similar to other studies<sup>5,39</sup>. There was no correlation found between sexual dysfunction and the other 3 sexual hormones that were studied: testosterone, estradiol and progesterone; data which confirms the results of previous studies<sup>39</sup>.

32% of patients met the criteria of metabolic syndrome, a percentage similar to the 35% of other studies also done with patients with schizophrenia<sup>23</sup>. Although there are studies of the general population that do associate sexual dys-

function with metabolic syndrome<sup>24</sup> or BMI, this correlation has not been found in our research.

Some studies suggest a relationship between sexual dysfunction and the severity of psychotic symptoms<sup>25</sup> or with negative symptoms of schizophrenia<sup>9</sup>, however our study has not found a relationship between psychotic symptoms (evaluated by PANSS) and sexual dysfunction. Regarding this, although our study did not exclude patients with severe psychopathology, its naturalistic design unintentionally favoured the inclusion of patients who were for the most part stable, with low PANSS scores (mean=50.8), which combined with the small size of our sample could indicate an inclusion bias. In spite of the equally moderate depressive symptomatology (HADRS, mean=5.9), inferior to the limit of 7 necessary to consider the existence of depression, it is still associated with sexual dysfunction. Of the 19 patients with HADRS scores >7 which satisfies the criteria for clinical depression according to this scale, 18 of them suffered from sexual dysfunction, with 10 of them suffering severe levels of dysfunction, thus confirming the correlation.

Table 4		Severity, Communication and Tolerance of Sexual Dysfunction		
	N	Mean (SD)	Percentage	
Salsex Total Score	57	4.26 (3.5)		
<b>Level of Severity</b>				
No dysfunction	11		19.3	
Mild	13		22.8	
Moderate	14		24.6	
Intense	19		33.3	
<b>Communication by the patient</b>				
Yes	17		29.8	
No	40		70.2	
Tolerance of dysfunction by the patient	57	1.17 (0.95)		
<b>Salsex Total Score by antipsychotics*</b>				
Aripiprazole	9	5.3 (4.5)		
Clozapine	7	3.7 (4.4)		
Olanzapine	18	4.1 (2.9)		
Risperidone/Paliperidone	22	4.3 (3.5)		

\* p value=0.86. Kruskal-Wallis Test

Table 5		PANSS and HDRS Scores	
	N	Mean (SD)	
<b>PANSS</b>			
PANSS-Positive	57	10.4 (3.8)	
PANSS-Negative	57	15.1 (5.6)	
PANSS-General Psychopathology	57	25.2 (4.3)	
PANSS-TOTAL	57	50.8 (9.9)	
<b>HDRS</b>			
Hamilton Total	57	5.9 (3.6)	
Hamilton >7	19	10 (1.8)	

Ong<sup>4</sup> finds no relationship between depression and sexual dysfunction. However, the sample in his study consists only of patients with schizophrenia in remission and only 17% exhibited symptoms of depression apart from symptoms of anxiety, approximating the normal range. Another study<sup>26</sup> does find a depression-sexual dysfunction association, though the patients were treated exclusively with

Table 6		Associated Factors of Sexual Dysfunction by Multivariate Lineal Regression		
		Multivariate Lineal Regression		
	b	95% IC Adjusted	p	
<b>Age</b>	0.130	0.054; 0.205	0.0012	
<b>Civil Status</b>				
Married/With Partner	0	1		
Single/Divorced	2.275	0.269; 4.280	0.0270	
<b>HDRS Score</b>	0.532	0.305; 0.759	0.0001	

risperidone for a period of at least 2 weeks, including inpatients as well as outpatients.

The other two variables that were linked to sexual dysfunction in our study were age and civil status (single or divorced). With b=0.13 for age (Table 6), this predicts that for every 10 additional years of age, sexual dysfunction (as evaluated by the Salsex) increases 1.3 points. Sexual impairment due to ageing has been reported in studies carried out in the general population<sup>40</sup> and in patients with schizophre-

nia<sup>26</sup>. Similarly to the general population, living with a sexual partner promotes better sexual functioning<sup>40</sup>. Our study, like others<sup>1,4</sup>, confirms the substantial difficulty that patients with schizophrenia have in living with a partner, with only 19% of our sample in this situation.

Two other results are worth mentioning: 20 patients refused to participate (the majority unwilling to answer questions related to their sexuality), and 17% of those who did participate had never maintained heteroerotic relations. This would seem to confirm that maintaining normal sexual functioning is difficult for patients with schizophrenia. This may have been present prior to the beginning of antipsychotic treatment<sup>20,22</sup>, or even the onset of the disorder itself<sup>25</sup>.

The most significant constraint on our study was the small size of the sample, a factor which could possibly skew the statistical results. Though an observational study, the number of patients that could be included was severely limited by the prerequisite of antipsychotic monotherapy and the exclusion of antidepressants and mood stabilisers. Another limitation was the non-randomised and observational structure of the study itself. This led to a sample comprised of generally stable patients, with moderate psychopathologies. More severe clinical profiles could influence the sexual functioning of these patients. A third limitation was the high number of patients who refused to participate in the study, explicitly refusing to discuss matters of sexuality despite having regular contact with their referring psychiatrists (the researchers in the study). The presence of this subgroup, which would be difficult to include in any study of sexuality, could theoretically modify the obtained results.

## CONCLUSIONS

The prevalence and severity of sexual dysfunction in outpatients with schizophrenia undergoing second generation antipsychotic monotherapy is high, even without receiving other psychiatric medications that may limit sexual functioning. Despite the existence of significant differences between the various antipsychotics in hyperprolactinemia and the existence of metabolic syndrome, neither prolactin nor metabolic alterations seem to influence sexual dysfunction. In our study, it was linked to ageing, living without a partner (single or divorced), and the presence of higher depressive symptomatology. In any case, it is possible that sexual dysfunction in schizophrenia may be caused by a complex combination of factors not well understood as of yet. Therefore, we believe new observational and randomised studies of sexual dysfunction in patients with schizophrenia are necessary, which include demographic, psychopathological and hormonal variables.

## ACKNOWLEDGEMENTS

Funding for this study was provided by PI 11/00569 from the Spanish Ministry of Economy and Competitive-

ness, co-funded by the Instituto de Salud Carlos III and by the European Regional Development Fund. These financiers had no influence on the design of the study; in the collection, analysis and interpretation of data and in the writing of the report.

## CONFLICT OF INTEREST

Dr. Martín participated in speakers/advisory boards for Boehringer Ingelheim, Eli Lilly, Janssen, Lundbeck, Otsuka and Pfizer. Dr. Acuña participated in speakers/advisory boards for Otsuka. Dr. Labrador, Blanco and Casas report no other financial relationship relevant to the subject of this article.

## REFERENCES

1. Montejo AL, Majadas S, Rico-Villademoros F, Llorca G, De La Gándara J, Franco M, et al.; Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. *J Sex Med.* 2010;7:3404-13.
2. Fuji A, Yasui-Furukori N, Sugawara N, Sato Y, Nakagami T, Saito M, et al. Sexual dysfunction in Japanese patients with schizophrenia treated with antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;34:288-93.
3. Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Psychopharmacol.* 2011;26:130-40.
4. Ong KY, Muhd Ramli ER, Che Ismail H. Remitted male schizophrenia patients with sexual dysfunction. *J Sex Med.* 2014;11:956-65.
5. Hanssens L, L'Italien G, Loze JY, Marcus RN, Pans M, Kerselaers W. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). *BMC Psychiatry.* 2008;8:95.
6. Rosenberg KP, Bleiberg KL, Koscis J, Gross C. A survey of sexual side effects among severely mentally ill patients taking psychotropic medications: Impact on compliance. *J Sex Marital Ther.* 2003;29:289-96.
7. Acuña MJ, Martín JC, Graciani M, Cruces A, and Gotor F. A comparative study of the sexual function of institutionalized patients with schizophrenia. *J Sex Med.* 2010;7:3414-23.
8. Chiesa A, Leucci V, Serretti A. Antipsychotics and sexual dysfunction: Epidemiology, mechanisms and management. *Clin Neuropsychia.* 2013;10:31-6.
9. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual Dys(function) in schizophrenia: an overview of clinically relevant findings. *Schizophr Bull.* 2015;41:674-86.
10. Just MJ. The influence of atypical antipsychotic drugs on sexual function. *Neuropsychiatr Dis Treat.* 2015;11:1655-61.
11. Olfson M, Uttaro T, Carson WH, Tafesse E. Male sexual dysfunction and quality of life in schizophrenia. *J Clin Psychiatry.* 2005;66:331-8.
12. Bebbington PE, Angermeyer M, Azorin JM, Marwaha S, Marteau F, Toumi M. Side-effects of antipsychotic medication and health-related quality of life in schizophrenia. *Acta Psychiatr Scand Suppl.* 2009;428:22-8.
13. Montejo AL, Montero C, Pol J, Esquer I, Romero O, Fernandez LC, et al. EPA-1652 Sexuality and emotional life in people with severe long-term mental disorders. *Eur Psychiatr.* 2014;29 suppl 1.



14. Ücok A, Incesu C, Aker T, Erkoc S. Sexual dysfunction in patients with schizophrenia on antipsychotic medication. *Eur Psychiatry*. 2007;22:328-33.
15. Bobes J, Garcia-Portilla MP, Rejas J, Hernandez G, Garcia-Garcia M, Rico-Villademoros F, et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: The results of the EIRE study. *J Sex Marital Ther*. 2003;29:125-47.
16. Montejo AL, Riesgo Y, Luque J, Barber Y. Estudio sobre la función sexual de pacientes que inician tratamiento con aripiprazol. Estudio naturalístico, abierto, prospectivo, multicéntrico. *Actas Esp Psiquiatr*. 2010;38:13-21.
17. Mesa N, de la Oliva J, Bagney A, Jimenez-Arriero MA, Rodriguez-Jimenez R. Agonismo parcial dopaminérgico en la disfunción sexual secundaria a antipsicóticos. *Actas Esp Psiquiatr*. 2013; 41:130-2.
18. Drago F, Pellegrini-Quarantotti B, Scapagnini U, Gessa GL. Short-term endogenous hyperprolactinemia and sexual behavior of me rats. *Physiol Behav*. 1981;26:277-9.
19. Zhang XR, Zhang ZJ, Zhu RX, Yuan YG, Jenkins TA, Reynolds GP. Sexual dysfunction in male schizophrenia: influence of antipsychotic drugs, prolactin and polymorphisms of the dopamine D2 receptor genes. *Pharmacogenomics*. 2011; 12:1127-36.
20. García-Rizo L, Fernandez-Egea E, Oliveira C, Justicia A, Parellada E, Bernardo M, Kirpatrick B. Prolactin concentrations in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. *Schizophr Res*. 2012;134:16-9.
21. Riecher-Rössler A, Rybakowski JK, Pflueger MO, Beyrau R, Kahn RS, Malik P, et al.; EUFEST Study Group. Hyperprolactinemia in antipsychotic-naïve patients with first-episode psychosis. *Psychol Med*. 2013;43:2571-82.
22. González-Blanco L, Greenhalgh AM, Garcia-Rizo C, Egea EF, Miller BJ, Kirkpatrick B. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: A meta-analysis. *Schizophr Res*. 2016;174:156-60.
23. Gutierrez-Rojas L, Azanza JR, Bernardo M, Rojo L, Mesa F, Martínez-Ortega JM. Prevalencia del síndrome metabólico en pacientes españoles con esquizofrenia y sobrepeso. El estudio CRESSOB. *Actas Esp Psiquiatr*. 2014;42:9-17.
24. Besiroglu H, Otunctemur A, Ozbek E. The Relationship Between Metabolic Syndrome, Its Components, and Erectile Dysfunction: A Systematic Review and a Meta-Analysis of Observational Studies. *J Sex Medicine*. 2015;12:1309-18.
25. Marques TR, Smith S, Bonaccorso S, Gaughran F, Kolliakou A, Dazzan P, et al. Sexual dysfunction in people with prodromal or first-episode psychosis. *Br J Psychiatry*. 2012;201:131-6.
26. Lee JY, Kim SW, Lee YH, Kang HJ, Kim SY, Bae KY, et al. Factors associated with self-rated sexual function in Korean patients with schizophrenia receiving risperidone monotherapy. *Hum Psychopharmacol*. 2015;30:416-24.
27. La Torre A, Giupponi G, Duffy D, Conca A. Sexual Dysfunction related to Psychotropic Drugs: A critical review-Part I: Antidepressants. *Pharmacopsychiatry*. 2013;46:191-9.
28. La Torre A, Giupponi G, Duffy DM, Pompili M, Grözinger M, Kapfhammer HP, et al. Sexual Dysfunction related to Psychotropic Drugs: A critical review-Part III: Mood Stabilizers and Anxiolytic Drugs. *Pharmacopsychiatry*. 2014;47:1-6.
29. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research. Geneva: World Health Organization; 1993.
30. Montejo AL, Rico Villademoros F. Psychometric properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRsexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. *J Sex Marital Ther*. 2008;34:227-39.
31. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261-76.
32. Peralta V, Cuesta MJ. Validación de la escala de los síndromes positivo y negativo (PANSS) en una muestra de esquizofrénicos españoles. *Actas Luso-Españolas de Neurología y Psiquiatría*. 1994;22:171-77.
33. Müller MJ, Rossbach W, Dannigkeit P, Müller-Siecheneder F, Szegedi A, Wetzel H. Evaluation of standardized rater training for the Positive and Negative Syndrome Scale (PANSS). *Schizo Research*. 1998;32:151-60.
34. Hamilton, M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6:278-96.
35. Micallef J, Fakra E, Blin O. Use of antidepressant drugs in schizophrenic patients with depression. *Encephale*. 2006;32:263-9.
36. Alberti KGM, Zimmet PZ, Shaw JE. The metabolic syndrome: a new world-wide definition from the International Diabetes Federation Consensus. *Lancet*. 2005;366:1059-62.
37. Nussbaum A, Stroup ST. Paliperidone for schizophrenia. *Cochrane Database Syst Rev*. 2008;16:CD006369.
38. Kikuchi T, Iwamoto K, Sasada K, Aleksic B, Yoshida K, Ozaki N. Sexual dysfunction and hyperprolactinemia in Japanese schizophrenic patients taking antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;37:26-32.
39. Yasui-Furukori N, Fujii A, Sugawara N, Tsuchimine S, Saito M, Hashimoto K, et al. No association between hormonal abnormality and sexual dysfunction in Japanese schizophrenia patients treated with antipsychotics. *Hum Psychopharmacol*. 2012;27:82-9.
40. Kontula O, Haavio-Mannila E. The Impact of Aging on Human Sexual Activity and Sexual Desire. *J Sex Res*. 2009;46:46-56.