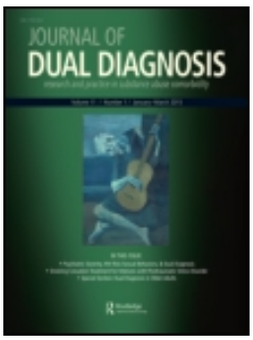

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Substance Use in Patients With First-Episode Psychosis: Is Gender Relevant?

Belen Arranz, MD, PhD,[1] Gemma Safont, MD,[2] Iluminada Corripio, MD, PhD,[3] Nicolas Ramirez, MD, PhD,[4] Rosa Maria Dueñas, MD,[1] Victor Perez, MD, PhD,[5] Enric Alvarez, MD, PhD,[2] and Luis San, MD, PhD[1]

Objective: Only a few studies in patients with first-episode psychosis have included gender in the study hypothesis or considered this a primary study variable. The aim of this study was to explore the influence of gender in the pattern of substance use in patients with first-episode psychosis. **Methods:** This is a sub-analysis of a randomized open clinical trial that compared 1-year treatment retention rates of patients with first-episode psychosis randomized to haloperidol, olanzapine, quetiapine, risperidone, or ziprasidone. Our sub-analysis included 85 men and 29 women. **Results:** Substance use was relatively high among these patients and differed significantly by gender. Men were more likely to use substances overall than women (89.4% for men vs. 55.2% for women), $\chi^2 = 16.2$, $df = 1$, $p < .001$, and were also more likely to use alcohol ($\chi^2 = 13$, $df = 1$, $p < .001$), cannabis ($\chi^2 = 9.9$; $df = 1$, $p < .002$), and cocaine ($\chi^2 = 10.3$; $df = 1$, $p < .001$), compared to women. While there were no gender differences in age at first consumption of alcohol or cocaine, men were significantly younger at first consumption of cannabis ($M = 16.08$ years, $SD = 2.1$) than women ($M = 18.0$ years, $SD = 3.8$), $F(1, 59) = 5$, $p < .02$. When analyzed separately by gender, women showed no significant differences in the influence of number of substances used on age at onset of psychosis, $F(3, 29) = 1.2$, $p = .30$. However, there was a significant difference among men, with earlier onset of psychosis noted in men consuming multiple substances; $F(4, 85) = 5.8$, $p < .0001$. Regarding prediction of age at onset of psychosis, both male gender and the use of a higher number of substances significantly predicted an earlier age at onset of psychosis. **Conclusions:** Our study provides some evidence of gender differences in the pattern of substance use in patients with first-episode psychosis, suggesting the possible need for gender-specific approaches in the interventions performed in these patients. This study is registered as #12610000954022 with the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au). (*Journal of Dual Diagnosis*, 11:153–160, 2015)

Keywords *substance use, first-episode psychosis, gender*

Although substance misuse is consistently reported in patients with first-episode psychosis, reliable clinical correlates of substance use in these patients have yet to be identified. Accumulated evidence indicates that concurrent substance use plays an important role in the development, course, and treatment of first-episode psychosis. Use of substances is associated with more pronounced positive symptoms, shorter duration of untreated psychosis, higher number of hospitalizations, reduced illness insight, increased medication and treatment non-adherence, higher service disengagement and relapse rates, poorer outcomes, and higher costs for mental health services (Large, Sharma, Compton, Slade, & Nielssen, 2011; Machielsen, van der Sluis, & de Haan, 2010; Sevy et al., 2001; Sevy et al., 2010; Donoghue et al., 2011; Mazzoncini et al., 2010; Compton, Whicker, & Hochman, 2007; Compton, Kelley, Ransay, & Pringle, 2009; Baeza et al., 2009; Barnett et al., 2007; Wade et al., 2006; Wade, Harrigan, McGorry, Burgess, & Whelan, 2007; Addington & Addington, 2007; Archie et al., 2007; Gonzalez-Pinto et al., 2008; Larsen et al., 2006; Van Mastrigt, Addington, & Addington, 2004; Lambert et al., 2005; Køster, Lajer, & Lindhardt, 2008; Schimmelmann, Conus, Cotton, McGorry, & Lambert, 2007; Verdoux, Tournier, & Cougnard, 2005). A reduction in substance use after diagnosis is associated with a reduction in subsequent admissions and psychotic symptoms (Lambert et al., 2005; Køster et al., 2008; Schimmelmann et al., 2007; Verdoux et al., 2005; Sorbara, Liraud, Assens, Abalan, & Verdoux, 2003). However, around three-quarters of patients with a lifetime history of substance misuse continue to misuse after the initiation of treatment (Wade et al., 2006). Alcohol

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and cannabis are the substances most frequently used in patients with first-episode psychosis (Van Mastrigt et al., 2004; Mauri et al., 2006).

Apart from using gender as a covariate or as a predicting factor in statistical analyses, a scarce number of studies involving patients with first-episode psychosis have included gender in the study hypothesis or as a primary variable in the study. To our knowledge, only nine studies have specifically assessed gender differences in first-episode psychosis (Køster et al., 2008; Cotton et al., 2009; Chang et al., 2011; Choi, Chon, Kang, Jung, & Kwon, 2009; Lange et al., 2014; Willhite et al., 2008; Mattsson, Flyckt, Edman, & Nyman, 2007; Thorup et al., 2007, 2014) and only one of them (Lange et al., 2014) has discussed the effect of gender in the pattern of substance use in this population. Delineating the relationship between gender and substance use in first-episode psychosis is of great importance in issues related to early detection, management, and therapeutic intervention of psychotic disorders. Therefore, the aim of this study was to further explore the influence of gender in the prevalence and pattern of substance use in patients with first-episode psychosis.

METHODS

Study Design

This study is the sub-analysis of a randomized open clinical trial designed to compare 1-year retention rates of patients with first-episode psychosis randomized to haloperidol, olanzapine, quetiapine, risperidone, or ziprasidone. Full details regarding screening, data collection, and standardized instruments are described elsewhere (San et al., 2012). The study was approved by the ethics committees of the participating hospitals. All participants received detailed written and oral information about the study and signed a consent document.

Participants and Setting

Patients were recruited between January 2004 and December 2007 in acute psychiatric units from three major hospitals located in the metropolitan area of Barcelona, Spain. The catchment area was approximately 1.5 million inhabitants.

To be included in the study, patients had to be older than 18 years, show psychotic symptoms at admission (having a score of 4 or more on the positive subscale items 1, 3, and 5 from the Positive and Negative Symptoms Scale [PANSS]) and be naïve of antipsychotic, antidepressant, or mood stabilizer treatment. The Structured Clinical Interview (SCID; Spitzer, Williams, Gibbon, & First, 1992) was used at 12-month follow-up to confirm *DSM-IV-TR* diagnoses.

Measures

Three sources of information were used to assess use of alcohol, cannabis, and cocaine: (a) Module E of the SCID, (b) individual clinical interviews with the patient and his/her closest relatives, and (c) urinalysis performed on admission to detect cannabis and cocaine. Patients using substances on a regular basis during the last 12 months, defined as three or more times per week for a period of at least one month, were rated as "substance users." All patients classified as using cannabis or cocaine showed a positive urine test result for the substance. Information about age at first substance use was obtained from the clinical interviews.

The duration of untreated psychosis was defined as the time from onset of the first psychotic symptom until initiation of the randomized antipsychotic (Norman & Malla, 2001). The variable "duration of untreated psychosis" was transformed (log 10) due to positive skewness (Tabachnick & Fidell, 2007). Age at onset of psychosis was considered to be the moment when the first psychotic symptom (hallucination/delusional belief/disorganized speech) appeared. The level of premorbid function was evaluated through the Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982). Psychopathological evaluation was performed through the PANSS (Kay, Opler, & Lindenmayer, 1989). Depressive symptomatology was evaluated through the Calgary Depression Scale for Schizophrenia (Addington, Addington, & Schissel, 1990).

Data Analysis/Statistical Procedures

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v15, Chicago, IL, USA). All statistical tests were carried out two-tailed, with an alpha level of significance set at $p < .05$. Categorical variables were compared with chi-square, and general linear modeling was used to test differences in the dependent variables between men and women. Bonferroni corrections were employed for post hoc comparisons between groups. An analysis of covariance was used to test differences between substance users and non-users in the dependent variables, with age and gender as covariates. A stepwise regression was performed to assess the variables predicting age at onset of psychosis (dependent variable).

RESULTS

As shown in Table 1, 114 patients were included in the study, 85 men and 29 women. Men were significantly younger than women; $F(1, 112) = 13.6$, $p < .001$, and were more often single (90.6% of men versus 58.6% women); $\chi^2 = 24.3$; $df = 3$, $p < .001$. Our sample did not show significant differences between men and women with regard to *DSM-IV-TR* diagnosis of schizophrenia/schizophreniform/schizoaffective disorder ($\chi^2 = 4.5$; $df = 1$, $p = .6$). Other diagnoses were psy-

TABLE 1
Baseline Demographical and Clinical Data ($N = 114$)

	Men $n = 85$	Women $n = 29$	
	M (SD)	*M (SD)*	
Age (years)	24.1 (5.9)	30.1 (11.2)	$F(1, 113) = 13.6; p < .001$
Partnership			
Single	77 (90.6%)	17 (58.6%)	$\chi^2 = 24.3; df = 3, p < .001$
Partner/spouse	8 (9.4%)	5 (17.2%)	
Divorced	0 (0%)	6 (20.7%)	
Widow	0 (0%)	1 (3.4%)	
Highest educational level			
Primary	37 (43.3%)	16 (55.2%)	$\chi^2 = 1.7, df = 2, p = .41$
Secondary	35 (41.2%)	8 (27.6%)	
High school	13 (15.3%)	5 (17.2%)	
Schizophrenia/schizoaffective disorder	56 (65.9%)	18 (62%)	$\chi^2 = 4.5; df = 1, p = .6$
	n (%)	*n* (%)	
DUP (weeks)	47.5 (115.1)	65.4 (266.9)	$F(1, 103) = 0.23; p = .63$
Log DUP	0.79 (0.73)	1.0 (0.76)	$F(1, 103) = 1.58; p = .21$
PAS	0.42 (0.24)	0.33 (0.19)	$F(1, 108) = 2.7; p = .10$
PANSS Positive	26.5 (6.1)	25.0 (6.3)	$F(1, 113) = 1.2; p = .25$
PANSS Negative	20.7 (8.8)	17.9 (9.6)	$F(1, 113) = 2.0; p = .15$
PANSS Total	92.5 (21.7)	88.2 (18.6)	$F(1, 113) = 0.88; p = .34$
CDSS	3.7 (4.5)	5.1 (4.8)	$F(1, 113) = 1.7; p = .18$
Alcohol use	72 (84.7%)	15 (51.7%)	$\chi^2 = 13; df = 1, p < .001$
Cannabis use	55 (64.7%)	9 (31.0%)	$\chi^2 = 9.9; df = 1, p = .002$
Cocaine use	24 (28.2%)	0 (0%)	$\chi^2 = 10.3; df = 1, p < .001$

Note. DUP = duration of untreated psychosis; PAS = Premorbid Adjustment Scale; PANSS = Positive and Negative Symptoms Scale; CDSS = Calgary Depression Scale for Schizophrenia.

chotic disorder not otherwise specified, bipolar disorder, brief psychotic disorder, and substance-induced psychosis. This last diagnosis was present in three patients. Weeks with psychotic symptoms prior to hospitalization ($F(1, 102) = 0.23, p = .63$, ANOVA), premorbid adjustment (PAS; $F(1, 107) = 2.7, p = .10$), PANSS positive ($F(1, 112) = 1.2, p = .25$), PANSS negative ($F(1, 112) = 2.0, p = .15$), PANSS total ($F(1, 112) = 0.88; p = .34$), and Calgary ($F(1, 112) = 1.7; p = .18$) scores did not show gender differences.

Gender and Substance Use

There was a significant gender difference with regard to current substance use, with 89.4% ($n = 76$) of the men reporting current consumption of any substance, as compared with 55.2% ($n = 16$) of the women; $\chi^2 = 16.2; df = 1, p < .01$. Regarding the specific substances consumed, 84.7% of men versus 51.7% of women consumed alcohol ($\chi^2 = 13; df = 1, p < .001$), 64.7% men versus 31% women consumed cannabis ($\chi^2 = 9.9; df = 1, p = .002$), and 28.2% of men versus 0% women consumed cocaine ($\chi^2 = 10.3; df = 1, p < .001$). Among all patients with cannabis consumption ($n = 64$; 55 men and 9 women), 92.7% ($n = 51$) of men and 55.6% ($n = 5$) of women were also alcohol users.

The number of substances currently consumed differed by gender as well, with 10.6% of men ($n = 9$) and 44.8% of women ($n = 13$) reporting no use, 22.4% of men ($n = 19$) versus 24.2% of women ($n = 7$) using one substance, 30.6% of men ($n = 26$) versus 27.6% of women ($n = 8$) consuming two substances, 17.6% of men ($n = 15$) versus 3.4% of women ($n = 1$) consuming three substances, and 18.8% of men ($n = 16$) and 0% of women consuming four substances ($\chi^2 = 21.7; df = 4, p < .001$; see Figure 1). Although a post hoc analysis was not performed, Figure 1 shows that women were more likely to not use any substance, while men were more likely to use three or more substances.

Age at first use of alcohol (16.06 years, $SD = 2.04$ in men vs. 15.7 years, $SD = 0.82$ in women; $F(1, 56) = 0.3$, $p = 0.58$) and cocaine (18.04 years, $SD = 0.99$ in men vs.

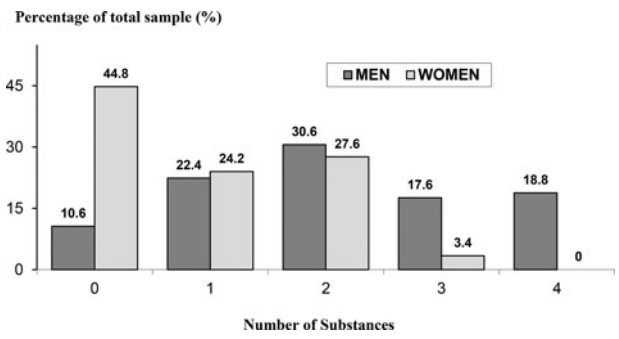

FIGURE 1 Number of substances used by gender ($N = 114$).

20.0 years, $SD = 0$ in women; $F(1, 25) = 3.7$, $p = .06$) did not differ significantly by gender. However, there was a statistically significant difference in age at first consumption of cannabis, with men initiating use at an earlier age than women (16.08 years, $SD = 2.1$ in men vs. 18.0 years, $SD = 3.8$ in women); $F(1, 59) = 5$, $p = .02$.

Gender and Substance Use Predicting Age at Onset of Psychosis

There was a trend toward significance for the interaction of gender and number of substances consumed on age at onset of psychosis; $F(3, 105) = 2.2$; $p = .089$. While this did not reach significance, we proceeded to examine the influence of number of substances on age at onset by gender because searching for these differences was one of the main outcomes of the study. As shown in Table 2, the number of substances consumed did not influence the age at onset of psychosis in women: no substance, 34.3 years ($SD = 13.5$); one substance, 25.1 years ($SD = 10.6$); two substances, 27.5 years ($SD = 4.8$); and three substances, 33.0 years ($SD = 0$ as there was only one woman consuming three substances); $F(3, 29) = 1.2$; $p = .30$. In contrast, a significant relationship was found in men, with earlier onset of psychosis noted in patients consuming multiple substances (no substance: $M = 27.5$ years, $SD = 7.5$; one substance: $M = 28.0$ years, $SD = 7.9$; two substances: $M = 23.4$ years, $SD = 4.4$; and three substances: $M = 20.4$ years $SD = 2.5$); $F(4,85) = 5.8$; $p < .001$.

Gender, use of substances, and number of substances used were entered in a stepwise regression model so as to test their ability to predict age at onset of psychosis (dependent variable). Two models were significant: The first model included the number of substances used in the last 12 months; $F(1, 113) = 23$; $p < .001$; while the second model included the number of substances used and being male; $F(2, 113) = 13.9$; $p < .001$. Therefore, being male and using several substances were the variables that most significantly contributed to an earlier age at onset of psychosis. All the other variables did not contribute to the overall significance of the model and were excluded from the analysis (see Table 3).

TABLE 3
Prediction of Age at Onset of Psychosis in Patients With First Episode Psychosis

	B	β	*p*	Overall model
Model 1				$F(1, 113) = 23$, $p < .001$; $R^2 = 0.17$
More substances used	−2.5	−0.41	.001	
Model 2				$F(2, 113) = 13.9$, $p < .001$; $R^2 = 0.20$
More substances used	−2.0	−0.33	.001	
Male gender	3.5	0.19	.018	

Note. B = unstandardized regression coefficient; β = standardized regression coefficient. R^2 = the amount of variance accounted for by the model.

DISCUSSION

Gender differences in patients with first-episode psychosis have been inconsistently reported in the medical literature in terms of illness onset, duration of untreated psychosis, course of disease, clinical variables, and prognosis (Cotton et al., 2009; Häfner et al., 1993; Lange et al., 2014; Chang et al., 2011; Choi et al., 2009; Willhite et al., 2008; Mattsson et al., 2007; Thorup et al., 2007, 2014; Køster et al., 2008; Melle et al., 2004; Pek, Mythily, & Chong, 2006).These discrepant results may be at least partially explained by methodological differences between studies, especially concerning the sample selection. Some studies have included both first episode schizophrenia and affective patients (Chang et al., 2011; Lange et al., 2014), and the two disorders may show up at different ages. Other studies that included only younger patients with first-episode psychosis (e.g., Chang et al., 2011; Cotton et al., 2009) may have missed many women with an older age at onset. With regard to duration of untreated psychosis, most studies have assumed that duration of untreated psychosis values follow a normal distribution instead of being positively skewed (Tabachnick et al., 2007), and therefore have not used the log-transformed value when perhaps it was needed. Study setting may also have accounted for differences between studies. Those conducted in hospital settings (Chang et al., 2011;

TABLE 2
Age at Onset (in Years) of First Episode Psychosis and Number of Substances Used ($N = 114$)

	Number of Substances Consumed					
	0 *M* (*SD*)	1 *M* (*SD*)	2 *M* (*SD*)	3 *M* (*SD*)	4 *M* (*SD*)	*F*(df), *p* Level
Men	27.5 (7.5)	28.0 (7.9)	23.4 (4.4)	20.4 (2.5)	22.06 (2.7)	$F(4, 85) = 5.8$; $p < .001$
Women	34.3 (13.5)	25.1 (10.3)	27.5 (4.8)	33.0 (0)[1]	—	$F(3, 29) = 1.2$; $p = .30$

Note. [1]One one woman reported using three substances.

Choi et al., 2009) likely enrolled patients with more severe onset, while studies conducted with community-based samples (Køster et al., 2008; Cotton et al., 2009; Lange et al., 2014; Willhite et al., 2008; Mattsson et al., 2007; Thorup et al., 2007, 2014) would tend to involve less severe cases. Due to these potential methodological differences, we cannot rule out the possibility that gender may be associated with substance use, duration of untreated psychosis, and age at onset of psychosis.

Gender and Substance Use in Patients With first-episode psychosis

Our reported rates of substance use by gender among patients with first-episode psychosis are in agreement with those reported in other studies. Cotton et al. (2009) indicated rates of overall substance consumption of 68% in men and 48% in women and rates of cannabis consumption of 52% in men and 36% in women. In the study by Mazzoncini et al. (2010) performed in 511 patients with first-episode psychosis, substance use rates were 70% in men and 30% in women, with 72% of male users and 28% female users consuming cannabis. Thorup et al. (2007, 2014), based on the Danish OPUS study performed in 578 patients with first-episode psychosis, reported rates of alcohol (36%) and cannabis (28%) use in women similar to ours. In the same study, cannabis use in men accounted for 51% of the total men's substance use, a percentage that agrees with that found in our sample. Lower rates of alcohol and cannabis use have been reported in three studies (Køster et al., 2008; Mattson et al., 2007; Lange et al., 2014), possibly because their population-based samples produced lower estimates of substance use than inpatient samples such as ours (Green, Young, & Kavanagh, 2005).

In our study, while no differences between men and women were noted in age at first consumption of alcohol and cocaine, age at first cannabis consumption was significantly lower in men. This is an important finding, as most studies reporting age at first consumption of a substance have not split the sample by gender (Sevy et al., 2001, 2010) and suggests increased cannabis exposure prior to onset of psychosis (Moore et al., 2007). A survey performed in the Spanish population within the same age range also showed that women started using cannabis at an older age than men and that patients with first-episode psychosis started using substances at a younger age than the general population (EDADES, 2006). Evidence indicates that cannabis use should be assigned a role in the pathogenesis of psychosis (Tosato & Lasalvia, 2009) and in predicting an earlier onset of schizophrenia (Veen et al., 2004). However, its effect may be confounded by the use of this substance in association with others. In our sample, alcohol use was present in 93% of men and in 56% of women using cannabis, and therefore the individual effect of cannabis could not be assessed. This finding is in line with other studies reporting that more than 50% of subjects using cannabis were polysubstance users (Sevy et al., 2001; Lambert et al., 2005).

In our sample, 28% of men versus 0% of women consumed cocaine. This finding may reflect both that patients usually underreport cocaine and amphetamine use in structured clinical interviews (Harrison, Haaga, & Richards, 1993) and that urinalysis performed at admission may have failed to detect cocaine consumption prior to the 3- to 5-day detection window. So far, none of the studies on substance use in patients with first-episode psychosis have specifically reported cocaine use by gender.

Age at Onset of Psychosis

Many studies on first-episode psychosis show that initiation of substance use typically precedes onset of psychosis, often by several years (Mauri et al., 2006; Rabinowitz et al., 1998; Veen et al., 2004; Buhler, Hambrecht, Loffler, Van der Heiden, & Häfner, 2002). Male gender and younger age have been frequently associated with substance use (Sevy et al., 2001, 2010; Wade et al., 2006; Cantwell et al., 1999; Rabinowitz et al., 1998; Buhler et al., 2002; Szymanski et al., 1995; Blanchard, Brown, Horan, & Sherwood, 2000). In our study, substance use was related to an earlier onset of psychosis in men but not in women, with the use of a higher number of substances also being associated with an earlier age at onset. Several studies have previously reported this finding, albeit without assessing a gender difference. For example, in the study by Carr, Norman, and Manchanda (2009), patients with first-episode psychosis using substances were on average 3.5 years younger at psychosis onset than non-users, and the use of cannabis reduced age at onset by 1.5 years (De Hert et al., 2011).

While most studies have assessed the use of cannabis in patients with first-episode psychosis, few studies have addressed the use of other substances (Veen et al., 2004; Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006). Studies investigating the effect of cannabis use on age at onset of schizophrenia have not always reported consistent results. Studies have found no significant association between cannabis use and age at onset (Sevy et al., 2001), earlier age at onset of psychosis in cannabis users independently of gender (Van Mastrigt et al., 2004; Mauri et al., 2006; Veen et al., 2004), and earlier age at onset for female but not for male patients (Rabinowitz et al., 1998). In the study by Veen et al. (2004) in 133 patients, male cannabis users had their first psychotic episode on average 6.9 years earlier than male non-users, and Barnes et al. (2006) reported male cannabis users having their first episode 4.2 years earlier than women and 5 years earlier than non-users. Other studies have also reported an earlier age at onset in cannabis-using patients, but not all of them corrected for gender differences (Addington & Addington, 2007; Gonzalez-Pinto et al., 2008). Although our study could not assess the individual effect of cannabis, our results indicate that the more substances used, the earlier the onset of psychosis. However, this effect was only present in men.

Strengths and Limitations

There are several strengths in the current study. We recruited a representative sample of never-treated patients with first-episode psychosis from three psychiatric services, including patients with severe substance use and/or severe psychosis. This is a very difficult population to recruit and more inclusive a range of clinical severity. Our study employed a variety of analytic methods, including multivariate analyses, to identify independent predictors of substance use disorders. We increased the potential validity of substance use classification by combining information from multiple sources (standardized and clinical patient interviews, supplemented by collateral information and urinalysis). Finally, we evaluated the possible contribution of alcohol and cocaine use, not just cannabis.

However, our findings should be interpreted in light of several methodological limitations. First, we acknowledge that the relatively small sample size may have impeded the detection of important associations between variables due to of lack of statistical power. The study only included people recruited from acute psychiatric units, therefore, more severely ill than community-based samples. As data on the frequency and amount of substance use were not available in this sample, differences between sporadic and heavy substance users could not be analyzed. Data on substance use (collected by self-report and family interviews and by urine analyses) was not corroborated by hair analyses, and synthetic drugs such as MDMA were not assessed. Furthermore, despite evidence on nicotine use being linked to the underlying biology of psychosis (Myles et al., 2012), information about nicotine use was not available for analysis. Cognitive performance of substance user patients as compared to non-users was not analyzed as it is the subject of another paper.

Conclusion

Our results confirm the high rates of substance use in patients first-episode psychosis and indicate the need to address the high prevalence of use of substances other than cannabis. Therefore, identification and reduction of substance use should then be a key target for all therapeutic strategies performed in patients first-episode psychosis (Wisdom, Manuel, & Drake, 2011). Our study also provides some evidence of gender differences in the pattern of substance use, suggesting the need for gender-specific approaches in all interventions performed in patients with first-episode psychosis, as well as specific substance use programs for men. Gender-specific interventions could enhance compliance, quality of treatment, and treatment success for both men and women. Our results also highlight the need for considering age at onset and gender as covariates in all statistical analyses involving substance use in first-episode psychosis. Because of an under-representation of women in previous clinical trials, more research should be conducted to investigate gender differences on treatment efficacy and side-effect profiles.

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DISCLOSURES

The authors declare that they have no competing interests in relation to this manuscript. Dr. Arranz has received honoraria for participating in expert meetings and conferences sponsored by Janssen, Eli Lilly, Servier, Otsuka, and Lundbeck. Dr. San has received honoraria for participating in expert meetings and conferences sponsored by Janssen, Eli Lilly, Ferrer, Servier, Bristol-Myers Squibb, Otsuka, and Lundbeck. Dr. Alvarez has received consulting and educational honoraria from several pharmaceutical companies, including Eli Lilly, Servier, GlaxoSmithKline, Sanofi, Lundbeck, and Pfizer. Dr. Perez has been a consultant and has received honoraria or grants from AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, Roche, Servier, and Medtronic. Drs. Safont, Corripio, Ramirez, and Dueñas report no financial relationships with commercial interests.

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