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(Article begins on next page)



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**Sex differences in first admission psychiatric inpatients with and without a comorbid
substance use disorder**

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Commento [HQ1]: The publisher asks for "(b) authors' full names, highest academic degrees, and affiliations"

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Running Title: Substance Use Disorder in Psychiatric Inpatients - a Gender-Tailored Approach

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Abstract

Objectives: We assessed gender differences in a sample of first-admission psychiatric inpatients with and without comorbid Substance Use Disorder (SUD) to identify possible risk factors and targets for gender-tailored treatment interventions.

Methods: A retrospective study of first admissions to the University Psychiatry Ward, “Maggiore della Carità” Hospital, Novara, Italy, between 2003 and 2012. The clinical charts of patients with (N=362) and without comorbid SUD (N=1111) were reviewed.

Results: Differences in employment, educational, and marital statuses were found between male and female psychiatric patients with and without comorbid SUD. Having a degree was a protective factor for males, while it was a risk factor for females. Being divorced and having family problems were both risk factors for comorbidity in females. Regarding the diagnosis, results overlapped in males and females, and both affective and other disorders were risk factors for a comorbid SUD.

Conclusions: A significant difference between male and female psychiatric patients with a comorbid SUD was the males’ overall poorer psychosocial functioning. Marital status and family problems were risk factors for comorbid SUD in females. Both males and females showed various pathways of access to and choices of substances and, eventually, experienced different impacts on their lives. Hospitalization might help to set up a targeted intervention for patients with comorbidity, while accounting for gender differences. With respect to males, a treatment approach focused on the substance alone might help improve their functioning; females might have a greater benefit from a treatment approach focused on distress, family problems, and relational issues.

The co-occurrence of severe mental health conditions with a drug abuse or dependence disorder (substance use disorder, SUD) is referred to as Dual Diagnosis (DD). Psychiatric patients with a comorbid SUD represent up to half of the patients in most mental health treatment systems, and comorbidity is associated with several significant implications with respect to symptoms, course, morbidity, treatment effectiveness and adherence, social issues (e.g. legal problems), use of psychiatric and emergency room services, and regrettably, with common negative outcomes (Owen et al., 1996; Kovasznay et al., 1997; Margolese et al., 2004; Ziedonis, 2004; Tosato et al., 2013).

The co-morbidity rate of SUD and major mental problems in Europe is generally not as high as in US according to various studies, and it ranges from 20% to 65% (Kessler et al., 1996; Teesson et al., 2000; Mueser et al., 2003). Additionally, comorbidity rates between psychiatric illness and SUD appear to be particularly high in inpatient, crisis team (38-50%), and forensic settings (Drake et al., 2004).

Comparisons between psychiatric patients with a comorbid SUD and those without show differences in socio-demographic, clinical, substance-related characteristics, and other background variables. For instance, Katz et al. (2008) found that comorbid patients were younger than non-abusers, and that they were more often males, unmarried, and of Western origin. In a multi-center European study about comorbidity between drugs and psychosis, researchers found that substance users were younger than non-users but that they did not significantly differ with respect to the other socio-demographic measures (Baldacchino et al., 2009). A comparison of patients with comorbid SUD, patients with SUD but no other mental disorder, and patients with mental disorders but no SUD showed several demographic and clinical differences and a higher risk for suicide in DD patients than in the other two groups (Szerman et al., 2012).

Moreover, gender differences have been described in psychiatric patients with comorbid SUD. First-episode psychotic female patients with a comorbid SUD seem to be particularly vulnerable, and, compared to men, they have shown a lower rate of SUD reduction at their one-year follow-up visits (Lange et al., 2014). Chronic alcoholic women tend to progress to treatment more quickly than men (Lewis and Nixon, 2013). Moreover, comorbidity has different patterns in men

and women with lifetime alcohol dependence: Antisocial personality disorder and other SUDs are more common in males, while mood and anxiety disorders are typical of females (Khan et al., 2013a). Similar gender differences were found in patients with a cannabis use disorder (Khan et al., 2013b) and with amphetamine-like stimulant abuse and ketamine abuse (Zhang et al., 2013). Alcoholic women, compared to alcoholic men, were more likely to report greater treatment barriers, including social stigmas (Khan et al., 2013a), while such differences were not found, for instance, in patients with cannabis use disorder (Khan et al., 2013b). Drapalski et al. (2011) suggested that by the time treatment is initiated, men and women with SUD tend to appear similar, but that prior to treatment-seeking, they were likely quite different. Differences with respect to the drug of choice and the pathway of abuse were reported (Gearon et al., 2003; Maremmani et al., 2010; Chen et al., 2011; Drapalski et al., 2011), and one fairly consistent gender difference has concerned the consequences of SUD, including physical health and legal problems (Brunette and Drake, 1997; Drapalski et al., 2011). However, current research has not yet fully addressed the issue of gender differences in psychiatric patients with comorbid SUD.

A complicating factor is that studies in this field tend to focus on different populations: the general public, the population of subjects referring to psychiatric services, and the population of people currently charged at addiction services (Rassol, 2002). This fact is a concrete reality in Italy. A parallel treatment for patients with comorbid psychiatric disorders and with SUD is a standard practice since mental health and addiction facilities have different institutional cultures, etiological concepts, administrative arrangements, and screening and treatment approaches (Carrà and Clerici, 2006). As a consequence, possible flaws in communication, collaboration and linkage might represent a significant barrier to comorbidity service delivery in Italy (Pozzi et al., 2008; Canaway and Merkes, 2010). Although it is clearly a growing problem with relevant clinical consequences and costs of care, the number of studies on DD prevalence in patients admitted to psychiatric wards in general hospitals in Italy is still scant. For instance, Picci et al. (2013) recently focused on differences in length of stay in first-hospitalization schizophrenic patients with and without comorbid SUD. Patients with comorbid SUD, they found, showed poorer symptom improvement

Commento [HQ2]: The expression “in charge of” means that they’re the boss—they manage the place. This is quite the opposite of being charged at, though this isn’t really the most clear way to express it either. Some other expressions are include: being checked in to, or being in residence at.

and required longer stays. In another study, Preti et al. (2009) reported that only about 30% of SUD patients discharged from acute psychiatric inpatient facilities (both public and private) were referred to drug addiction services. Furthermore, Testa et al. (2013) assessed SUD in emergency settings, and Bizarri et al. (2009) and Maremmani et al. (2011) looked into whether the SUD tends to follow or to predate the psychiatric diagnosis. Nonetheless, no Italian study has yet specifically focused on gender differences of inpatients with and without a comorbid SUD.

The objectives of this study were the following: 1) to assess the extent of drug abuse in a sample of patients at their first admission to a psychiatric inpatient ward in a general hospital in Italy; 2) to investigate gender-related differences in patients with and without a comorbid SUD, focusing on socio-demographic, clinical, and other background variables; 3) to investigate gender differences with respect to risk factors for comorbid SUD in order to identify possible gender-specific targets for interventions.

Methods

An observational retrospective study was performed that involved reviewing clinical charts of patients first admitted to the Institute of Psychiatry, Inpatient Unit, “Maggiore della Carità” Hospital, Novara, Italy. The period of study was from 2003 to 2012. Patients with a discharge diagnosis of SUD but no comorbid psychiatric disorder were excluded, and the researchers focused on DD patients (PSY-SUD) and psychiatric patients without comorbid SUD (PSY).

The following information was retrieved from the clinical charts:

1. Socio-demographic data, including age, gender, education, occupational status, living accommodations, marital status, and legal problems;
2. Family history, with a specific focus on stressful situations including parental loss or divorce, occupational and/or financial problems, psychiatric and/or SUDs, parents’ legal problems;
3. Clinical and psychopathological history including information concerning drug use, when their first diagnoses were received (psychiatric, SUD, both), comorbid organic disorders, history of self-harm including suicidal and para-suicidal behaviors, history of aggressive behaviors and

acting out, and the number of inpatient admissions in the year following the first admission to the psychiatric ward.

Psychiatric diagnoses were made by experienced psychiatrists with the aid of the Structured Clinical Interviews I (First et al., 2000) and II (First et al., 2003), for Axis I and Axis II disorders, respectively. In accordance with the International Classification of Diseases (ICD-9) (World Health Organization, 2002), diagnoses were the following: organic and substance-induced psychoses (ICD 290-294), other psychoses (ICD 295, 297, 298), affective disorders (ICD 296), neurotic disorders (ICD 300), and personality disorders (ICD 301). Disturbance of conduct, mental retardation, eating disorders, acute stress reaction, and adaptation reaction were grouped as “other diagnoses” (ICD 307-312, 317-319).

Commento [HQ3]: Organic-induced or just organic? (If the former, then write organic- and substance-induced psychoses. If the latter, leave as is now.)

With respect to the use of psychotropic drugs, data about age at first use and type of substance used were also gathered from the clinical charts (data not shown).

The research project was approved by the Institutional Review Board of Università del Piemonte Orientale.

Statistical analysis

Statistical analyses were carried out using STATA 11 (Stata Corp., College Station, TX, 2011). Initial descriptive statistics included the Chi-squared test to evaluate the differences in proportions between groups (PSY-SUD vs. PSY patients). Then a multivariate analysis was performed using a logistic regression to assess the potential predictors of SUD. The covariates included in the final model were selected using a stepwise forward selection process, with a univariate p-value <0.25 as the main criteria (Hosmer and Lemeshow, 1989). Separate models for the univariate and multivariate analyses were performed for males and for females. Results are expressed as Odds Ratio (OR) with 95% Confidence Intervals (CI). A two-tailed p-value <0.05 was considered significant for all analyses.

Results

We sourced data from 1,473 patients' first admission to the Psychiatry Ward that fulfilled the inclusion criteria described above. Males (N=654) comprised 44% of the sample, and females (N=819), 56%. The overall number of PSY-SUD subjects was 362 (24.6% of the total sample), of whom 242 were males (37% of the male sample; 67% of the DD group), and the remaining 120 were females (14.6% of the female sample). The mean age of the whole sample was 44 with a standard deviation (SD) of ± 16.4 years.

We grouped patients according to gender for the statistical analyses, and each group was further subdivided according to comorbid SUD (yes or no). PSY-SUD and PSY patients' socio-demographic and clinical variables were compared. Results are reported in Tables 1 and 2, respectively.

Statistically significant differences were found between male and female patients with a PSY-SUD and PSY diagnosis regarding employment, education, and marital status. The accommodation statuses were different between PSY-SUD and PSY female patients. Family problems were more common in PSY-SUD patients; PSY-SUD males were less likely to have children and had a lower educational level than PSY males. However, the opposite result was found in the female sample. Although the rate of unemployment was higher in both male and female PSY-SUD patients, a difference was found between males and females regarding employment. PSY-SUD males were less likely to have a job than were PSY males; however, PSY-SUD females were more often employed than PSY females.

A significant difference was found in males regarding violence and legal problems; both conditions were more common in PSY-SUD than in PSY patients. In females, self-harm behaviors were significantly more common in PSY-SUD than in PSY patients.

Table 1 and Table 2

Results from the univariate and multivariate analyses for males and females are shown in Tables 3 and 4, respectively. In both genders, some risk and protective factors for comorbid SUD were identified among the assessed socio-demographic and clinical variables.

In males, having a degree was more of a protective factor than just having attended primary school (OR= 0.30; 95%CI 0.10-0.92; p= 0.036). Regarding occupation, the reference category was “being unemployed,” and being disabled was a protective factor (OR= 0.28; 95%CI 0.11-0.70; p= 0.007). No other category maintained statistical significance in the multivariate analysis. With respect to diagnosis, both affective disorders and “other” disorders were risk factors for a comorbid SUD, while having a personality disorder was not a risk factor (OR= 3.24; 95% CI 1.53-6.85; p= 0.002; OR= 2.64; 95%CI 1.26-5.52; p= 0.010).

Commento [HQ4]: If this is not what you mean, indicate what the comparison was. Less of a risk factor?

Some other variables were found to be risk or protective factors in the univariate analysis, but were no longer significant after the multivariate analysis (including being single or divorced, having family problems, acting in harmful ways, and having legal problems as risk factors, and having children as a protective factor; see Table 3 for further details).

In females, having a degree was a risk factor for both PSY-SUD and PSY patients (OR= 7.52;95%CI 2.75-20.61; p< 0.001), and being divorced and having family problems were both risk factors for PSY-SUD patients (OR=3.69; 95%CI 1.83-7.42; p< 0.001; OR=2.75; 95%CI 1.69-4.48; p< 0.001). Regarding diagnoses, results were similar to those found among males, and both affective and “other” disorders were risk factors for PSY-SUD diagnoses (OR= 4.85; 95%CI 1.94-12.08; p= 0.001; OR= 3.01; 95%CI 1.16-7.82; p= 0.024). Age was a protective factor (OR= 0.97; 95%CI 0.94-0.99; p= 0.037).

Commento [HQ5]: I assume ?

Finally, both in females and in males, some variables were found to be risk or protective factors in the univariate analysis, but were no longer significant after the multivariate analysis (including being retired and being a housewife as protective factors and having divorced parents and performing acts of self-harm as risk factors; see Table 4 for further details).

Table 3 and Table 4

Commento [HQ6]: Name it instead of saying "our"

Discussion

PSY-SUD patients who were first admitted to the psychiatric ward represented 24.6% of the total sample. Results from similar studies display a wide variability, ranging from 24% to 51% (Weich and Pienaar, 2009; Katz et al., 2008). Our findings are consistent with previous reports from mental health and addiction services in Italy that have described a prevalence of psychiatric disorders with comorbid SUD, ranging from 4% (data from mental health departments) to 42% (data from addiction services) (Di Furia et al., 2005; Siliquini et al., 2005; Zeppegno et al., 2005; Zeppegno et al., 2009; Relazione annuale al Parlamento sullo stato delle tossicodipendenze in Italia, 2012).

In our sample, 47.5% and 49.1%, respectively, of the PSY-SUD and PSY patients had received a psychiatric diagnosis prior to their inpatient admission. Therefore, more than half of the patients were admitted to the psychiatric ward without having previously been charged to any mental health service.

Consistent with previous reports about patients with comorbid psychiatric disorders and SUD (Di Furia et al., 2005; Katz et al., 2008; Rodríguez-Jiménez et al., 2008; Weich and Pienaar, 2009; Relazione annuale al Parlamento sullo stato delle tossicodipendenze in Italia, 2012), PSY-SUD patients in our sample were mainly males (242 versus 120 females), younger at admission, and more commonly divorced than PSY patients.

Gender differences between PSY-SUD and PSY patients

The chi-square comparison of the PSY-SUD and PSY patients highlighted statistically significant differences in education, occupation, and marital status, in both males and females, which facts support the hypothesis of possible differences in the social functioning and performance of both male and female PSY-SUD patients (Miquel et al., 2011), with the former performing worse. Their performance might also depend on the fact that some disorders, such as psychotic disorders, onset at different ages in males than in females. We should also point out that in our analyses, patients were not grouped according to their main substance or patterns of abuse, which

are likely to be different across genders (Maremmani et al., 2010; Brunette and Drake, 1997; Drapalski et al., 2011) and also likely to impact the patients' education and work attainment. Furthermore, female PSY-SUD patients were more likely than PSY patients to live alone or with their parents, whereas they were less likely to live with a family of their own. Male PSY-SUD patients were less likely than PSY patients to have children.

Based on the chi-squared analysis performed on our sample, we found that PSY-SUD male patients were significantly more likely than PSY male patients to have a history of aggressive behaviors and legal problems, and PSY-SUD female patients were more likely than PSY females to have a history of self-harm behaviors. In the univariate analysis, violent behaviors emerged as risk factors in males, and self-harm behaviors as risk factors for comorbid SUD in females. In the multivariate analysis, we did not find violent, self-harm behaviors, or legal problems as risk factors for a comorbid SUD, neither in males nor in females. Additionally, such behaviors might be a consequence rather than a possible risk factor for comorbidity.

Risk and protective factor for SUD in male and female patients

In the univariate and multivariate analyses, we found partially different patterns of risk and protective factors for comorbid SUD in male than in female patients. Shared risk factors for comorbid SUD included diagnosis, which will be discussed later.

However, opposite results were found between males and females regarding their educational levels: While having a degree was a protective factor for males, it was a risk factor in females. As described in the previous section, this result supports a different pattern of social functioning and performance in male than in female PSY-SUD patients (Miquel et al., 2011). Males were likely to have worse social functioning, and an indicator of good achievement, such as having a degree, represented a protective factor for them. On the other hand, women were likely to perform well, yet this better performance could be intertwined with the risk of distress and of a consequent substance use. This result supports the suggestion that males and females accede to substances via

different pathways and choose different types of substances (Gearon et al., 2003; Maremmani et al., 2010; Chen et al., 2011; Drapalski et al., 2011), with variable impacts on their lives.

In our sample, marital status and family problems were relevant risk factors for comorbid SUD only in females: Being divorced and having family troubles exposed females to a higher risk of comorbidity. These patients seemed to experience relational problems in their families and to have difficulties either creating or maintaining lasting relationships. On the other hand, comorbidity of psychiatric disorders and SUD alone might have impacted their relationships. Interestingly, this seemed particularly important in females. Such issues have recently received more attention; for instance, the object of a study by Macy et al. (2013) suggested that partner violence and substance abuse in women were interconnected.

With respect to the psychiatric diagnosis in patients with and without comorbid SUD, results from the univariate and multivariate analyses suggested that in both genders, affective and “other” disorders were risk factors for comorbid SUD, compared to personality disorders, which were chosen as reference category because they were more likely than Axis I disorders to be associated with chronic SUD (Baigent, 2012).

Commento [HQ7]: What did the comparison reveal? More? Less? “In comparison” or “compared to” need to accompany a more or less, greater than or less than, etc.

Recently Arias et al. (2012) reported that comorbid SUD were equally common in schizophrenic psychoses and in personality disorders, but also that people with primary mood or anxiety disorders were at a high risk for comorbid SUD (Osuch et al., 2013; Wu et al., 2013; Torchalla et al., 2013). It should be remembered that SUD might increase the odds of subsequent mood disorders (Kenneson et al., 2013), and clinicians should control early on for SUD in patients with anxiety and mood disorders (Baigent, 2012) in order to avoid the revolving-door effect, which might depend on the substance used (for example, psychotic symptoms elicited by cannabis abuse in vulnerable subjects) (Arias et al., 2012; Lange et al., 2014; Chen et al., 2013).

Limitations

The retrospective design and data gathering through clinical records entail some limitations. Some information was unavailable, for example data about race and detailed descriptions of types

of self-harm or aggressive behavior. We reported no data about laboratory tests objectively detecting drugs. Additionally, Latt et al. (2011) suggested that a urine drug screening can only identify a small additional rate (5%) of substance users. Moreover, since our objective was to take a “snapshot” of comorbidity in the psychiatric ward, we neither discussed data about the type of substance used, nor did we gather information concerning “acute” reasons for inpatient admission or voluntary or compulsory admission, nor did we examine in detail service-use data and the time correlation between drug abuse and the occurrence of major mental problems (Maremmani et al., 2010). However, we gathered information about the patients’ having previously received psychiatric diagnoses.

On the other hand, the large sample size is a strong point of this research, which adds to the paucity of studies concerning this issue in Italy.

Conclusions

Both psychiatric disorders and SUD are predictors of underachievement and failure in educational and occupational settings, difficulty facing family responsibilities, violent and abusing behaviors, poverty, legal problems, and scarce compliance to treatment (Kessler et al., 1996). Regarding gender differences, Najt et al.’s (2011) recent review of potential predictors of co-occurring mental disorders and SUD focused on the more common negative outcomes in male patients, associated with major depression and the number of psychiatric diagnoses.

A more in-depth analysis of gender differences in psychiatric patients with comorbid SUD might be helpful, if such a study also considered that the two genders respond differently to the treatment approaches addressed to such disorders (Baigent, 2012).

In our sample, we found differences between male and female PSY-SUD and PSY patients, including differences in socio-demographic and clinical variables. These results are not easily compared with those presented in existing literature as this issue has not yet fully been addressed due to inconsistencies of the studied samples. Our results, however, support the general statement about fairly consistent differences in the consequences and impact of substance use in males and in

females (Brunette and Drake, 1997; Drapalski et al., 2011), with the former showing poorer achievements in education and in occupation.

Regarding risk and protective factors, males and females showed different profiles, and, interestingly, a high educational achievement seemed to have a different impact on comorbid SUD according to gender. Family problems and being divorced were risk factors for comorbid SUD in females but not in males.

Barriers to treatment seemed to be similar for both genders (Chen et al., 2013), but it is likely that different approaches are needed for male and female patients with comorbid psychiatric disorders and SUD. With respect to males, as we found no particular risk factor for comorbidity, it is likely that a treatment approach focused on the substance alone might help improve their functioning, as Baigent (2012) already suggested. On the other hand, females might have a greater benefit from a treatment approach focused on family problems and relational issues, and also on the distress derived from good educational and occupational achievements, which ideas are in accordance with Grella (2003)'s study describing a greater need for family and trauma-related services in females.

Acute settings might be particularly appropriate for the development of targeted interventions (Carrà and Johnson, 2009), and the treatment of patients with comorbid psychiatric disorders and SUD, also allowing for gender differences, should begin early during hospitalization (Bradizza and Stasiewicz, 1997).

Ethical Standards

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Commento [HQ8]: The style guide provided by the publisher doesn't require the hanging indent, but the straight double spacing with no space between entries can be a little hard on the eyes. Feel free to undo it, but the style guide doesn't seem to forbid it either.

Commento [HQ9]: The publisher asks that if it's in press, you write "in press." If it hasn't been accepted for publication, then it doesn't go on the List of References page. If this refers to something else, just pick the medium you used. It's not necessary to identify all of the media in which a publication is available. If you used the electronic version, follow this format:

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Commento [HQ10]: You'll have to find the abbreviations for the journal titles.

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