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ORIGINAL ARTICLE

## The prevalence of comorbid anxiety disorders in outpatients with schizophrenia

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### Abstract

**Objective.** The purpose of this study was to determine the prevalence of lifetime anxiety disorders in patients with schizophrenia in Sanliurfa, Turkey, and to assess the association between comorbidity and several demographic and clinical variables. **Methods.** Eighty-two outpatients diagnosed with schizophrenia were recruited for the study. They were assessed by means of the Structured Clinical Interview for DSM-IV axis I Disorders–Clinician Version (SCID-I-CV), Anxiety Disorder Module, the Positive and Negative Syndrome Scale (PANSS), the Hamilton Anxiety Rating Scale (HARS), and the Global Assessment of Functioning Scale (GAF). **Results.** Fifty-five (67.1%) were diagnosed with at least one lifetime comorbid anxiety disorder. The most common anxiety disorder was obsessive-compulsive disorder (39.0%), followed by social phobia (13.4%). We found patients with a diagnosis of schizophrenia with comorbid anxiety disorders had shorter duration of illness than those without such comorbid conditions. Atypical antipsychotics were more commonly prescribed to treat these patients. **Conclusion.** As comorbidity of anxiety disorders is relatively prevalent among patients with a diagnosis of schizophrenia, special attention to this issue should be paid when interviewing these patients.

**Key Words:** Schizophrenia, comorbidity, anxiety disorders, obsessive-compulsive disorder, social phobia

### Introduction

The topic of comorbid anxiety disorders in schizophrenia is somehow neglected in the literature. Clinical and epidemiological studies have proved that comorbid anxiety disorders are relatively prevalent among patients with schizophrenia, and they are found in up to 60% of cases [1–5]. Comorbidity of anxiety disorders may be associated with greater suicidal disposition, substance abuse, resistance to pharmacological treatment, increased risk of relapse, poorer social functioning and poor outcome [6–8].

Despite the fact that anxiety has long been recognized as an important part of the psychopathology of schizophrenia, there is a paucity of data regarding the occurrence of anxiety symptoms or syndromes in schizophrenia. An important reason for this is that the operational criteria for psychiatric diagnoses suggest that disorders hierarchically lower should not be added as comorbidities to the main diagnosis. This idea prevents

clinicians and researchers from paying adequate attention to the accessory symptoms shown by these patients outside of the core positive–negative disorganized symptoms [9].

The purpose of this study was to determine the prevalence of lifetime anxiety disorders in a sample of clinically stable outpatients with schizophrenia and to assess the association between comorbidity and several demographic and clinical variables. This study provides a view of lifetime anxiety disorder comorbidity in patients with schizophrenia in Sanliurfa, Turkey.

### Methods

#### Participants

All patients assessed at the Schizophrenia and Other Psychotic Disorders Outpatients Clinics of Harran University, Sanliurfa, Southeastern Turkey, between

2004 and 2006, were considered for inclusion in the study. Patients diagnosed with schizophrenia in the psychiatric clinics of Harran University Research Hospital (a tertiary level health institute which receives referrals from the southeastern part of Turkey) were recruited for the study. Among patients enrolled in this unit, those who met the following criteria were included in the study: (1) age of at least 18 years; (2) DSM-IV diagnosis of schizophrenia; and (3) written informed consent obtained before participation in the study. The diagnosis of schizophrenia was clinically made according to DSM-IV criteria on admission of the patient to the follow-up routine of outpatient clinics and later confirmed by interviews conducted by the first and the second authors. Exclusion criteria were: (1) history of seizure, head injury with loss of consciousness, or other neurological disorder; (2) not being capable of understanding and filling out forms and questionnaires; (3) unwillingness to cooperate with investigators; and (4) contact loss.

Among the 124 cases who were enrolled in our schizophrenia and other psychotic disorders outpatient clinic, 82 patients (19 females, and 63 males), aged between 18 and 67 years, fulfilled the inclusion criteria for the study. Our sample included 58 patients (71%) discharged from in-patient care and 24 patients (29%) who only received out-patient care. Out of 124 patients, 13 had other psychotic disorders (i.e. delusional disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder and psychosis not otherwise specified), one had a history of seizure, two had mental retardation, three did not wish to be interviewed, and 23 were lost to follow-up. These cases, therefore, were excluded from the study. The study protocol was approved by the Local Ethics Committee of the Harran University Faculty of Medicine.

### Measures

1. Socio-demographic and clinical variables of the subjects including previous hospitalizations, suicide attempts and age of onset of the disorder were obtained from inpatient and outpatient medical records of the cases, patient interviews, and from first-degree relatives when available. Additionally, we investigated the use of special modalities of treatment such as atypical antipsychotic drugs, anti-anxiety medications, and ECT.
2. The Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-I-CV), Anxiety Disorder Module was used to

diagnose lifetime comorbidities of anxiety disorders. SCID-I is a semi-structured clinical interview scale that was developed to diagnose major DSM-IV Axis-I disorders [10]. In the validity and reliability studies of SCID-I in Turkey, for the interviewers' all diagnoses, the consistency ratio was found as to be 98.1% and the kappa ( $\kappa$ ) coefficient as to be 0.86 [11]. All patients were interviewed by the first author, trained in the use of the SCID-I. Individuals who were found to present at least one lifetime anxiety disorder were included in the group "with comorbid anxiety disorder", and those without any comorbid anxiety disorder, in the group "without comorbid anxiety disorder".

3. The Positive and Negative Syndrome Scale (PANSS) [12] has 30 items classified into three subsections, positive symptoms such as hallucinations, delusions and hostility; negative symptoms such as blunted affect, withdrawal, passivity, and difficulty in abstract thinking; and general emotional disturbances such as anxiety, depression and guilt. Kostakoğlu et al. [13] conducted reliability and validity studies of the Turkish version of the scale.
4. The Hamilton Anxiety Rating Scale (HARS), which was developed by Hamilton [14], is a semistructured interview containing 14 items which assess the severity of anxiety symptoms. The scale consists in two factors (general psychological anxiety symptoms and cognitive symptoms) and is rated on a five-point scale, with 5 being the worst. Yazici et al. [15] confirmed the validity of the Turkish version.
5. The Global Assessment of Functioning Scale (GAF) [16] was applied to assess the patients' psychosocial functioning. The GAF is a 100-point single-item scale that rates functioning on a hypothetical continuum of mental health to mental illness. The scale values range from 1 (representing the hypothetically most impaired individual) to 100 (the hypothetically healthiest individual), with 0 used only when there is inadequate information. The scale is divided into 10 equal intervals. The anchor point descriptions of each 10-point interval define the scale. For each scale, a single number comprises the final score.

The scales other than SCID-I were administered by the first author. All patients were interviewed within a period of 14 months, from March 2005 to June 2006. Every interview session had a duration between 30 and 60 min.

*Statistical analysis*

The Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc, Chicago, IL) was used for all statistical analyses. Normality of quantitative data was checked using the Kolmogorov–Smirnov one-sample test. Differences between groups were tested by *t*-test and Mann–Whitney *U*-test for normal and non-normal continuous variables, respectively, and chi-square test for categorical variables. The two-tailed significance level was set at 0.05.

**Results***Anxiety disorder comorbidity*

Fifty-five (67.1%) of the 82 patients in the sample, were diagnosed with at least one lifetime comorbid anxiety disorder. Of the 67.1% diagnosed with any anxiety disorder, 67.2% (45.1% of total sample) were found to have a single anxiety disorder, 32.7% (21.9% of the total sample) had two anxiety disorders, and 1.8% (1.2% of the total sample) had three anxiety disorders. The most common anxiety disorder in this sample, based on frequency, was obsessive-compulsive disorder (39.0%,  $n=32$ ), followed by social phobia (13.4%,  $n=11$ ), specific phobia (9.7%,  $n=8$ ), panic disorder (8.5%,  $n=7$ ), generalized anxiety disorder (8.5%,  $n=7$ ), posttraumatic stress disorder (7.3%,  $n=6$ ), agoraphobia without panic disorder (2.4%,  $n=2$ ), and anxiety disorder not otherwise specified (1.2%,  $n=1$ ).

*Socio-demographic characteristics*

The socio-demographic characteristics of the two groups are provided in Table I. The patients were predominantly male, middle-aged, and unmarried.

The sample had a relatively good educational level, with 50% of the research subjects having at least some secondary education. However, less than 20% of all patients were working at the time of the assessment. Mean age was significantly lower in the group with comorbid anxiety disorders ( $t = -2.28$ ,  $df = 80$ ,  $P = 0.02$ ).

*Clinical characteristics*

The clinical characteristics of the two groups are provided in Table II. The sample included 46 patients with the paranoid subtype of schizophrenia, one with the disorganized, eight with the undifferentiated, and 27 with the residual type.

All patients were under antipsychotic pharmacological treatment, with 70.7% of them receiving atypical drugs. Atypical antipsychotics were significantly more common, being used by the patients with comorbid anxiety disorders ( $\chi^2 = 6.93$ ,  $P = 0.008$ ). The most frequently prescribed medications in our patient group were conventional antipsychotics (32 patients (39.0%)), followed by olanzapine (23 patients (28.0%)), and risperidone (19 patients (23.1%)). Few patients were prescribed quetiapine (nine patients (10.9%)), clozapine (five patients (6.0%)) or ziprasidone (two patients (2.4%)). There were no other statistically significant differences between the two groups regarding clinical features.

**Discussion**

Our results on the rates of comorbidity (67.1% of patients had at least one comorbid diagnosis) are comparable to the rates reported elsewhere [1–5,9]. Among anxiety disorders, OCD was the most

Table I. Patients with a diagnosis of schizophrenia with and without comorbid lifetime anxiety disorders: socio-demographic characteristics.

	With comorbid anxiety disorders ( $n=55$ )	Without comorbid anxiety disorders ( $n=27$ )	$U^a/t/\chi^2$	<i>P</i>
Age ( $\pm$ SD) [years]	31.8 $\pm$ 8.9	37.1 $\pm$ 11.4	-2.28	0.02
Education ( $\pm$ SD) [years]	7.9 $\pm$ 4.0	9.2 $\pm$ 4.3	-1.38	NS
Gender			0.02	NS
Male	76.4%	77.8%		
Female	23.6%	22.2%		
Marital status			0.004	NS
Married	36.4%	37.0%		
Non-married or divorced	63.6%	63.0%		
Currently working			0.14	NS
Yes	18.2%	14.1%		
No	81.8%	85.2%		

<sup>a</sup>Mann–Whitney test; SD, standard deviation; NS, not significant.

Table II. Patients with a diagnosis of schizophrenia with and without comorbid lifetime anxiety disorders: clinical characteristics.

	With comorbid anxiety disorders (n=55)	Without comorbid anxiety disorders (n=27)	$U^a$ / $t/\chi^2$	P
Age of onset ( $\pm$ SD) [years]	21.5 $\pm$ 4.6	21.5 $\pm$ 5.7	0.02	NS
Duration of illness ( $\pm$ SD) [years]	10.2 $\pm$ 8.4	15.5 $\pm$ 10.5	-2.51	0.01
Number of hospitalizations ( $\pm$ SD)	2.6 $\pm$ 2.6	2.6 $\pm$ 2.0	-0.52	NS
PANSS positive score ( $\pm$ SD)	13.1 $\pm$ 4.0	12.0 $\pm$ 5.0	1.15	NS
PANSS negative score ( $\pm$ SD)	18.4 $\pm$ 5.3	20.0 $\pm$ 5.7	-1.17	NS
PANSS general emotional disturbance score ( $\pm$ SD)	26.8 $\pm$ 3.9	26.9 $\pm$ 4.3	-1.11	NS
PANSS total score ( $\pm$ SD)	58.6 $\pm$ 9.7	58.9 $\pm$ 9.9	-0.10	NS
HARS score ( $\pm$ SD)	6.3 $\pm$ 3.3	5.3 $\pm$ 2.7	-1.13	NS
GAF score ( $\pm$ SD)	60.7 $\pm$ 5.7	60.7 $\pm$ 8.7	-0.64	NS
Subtype of schizophrenia				
Paranoid	63.6%	40.7%		
Disorganized	1.8%	-		
Undifferentiated	9.0%	11.1%		
Residual	25.4%	48.1%		
Mode of onset			1.82	NS
Acute	49.1%	29.6%		
Non-acute	50.9%	70.4%		
Personal history of suicide attempts			0.52	NS
Yes	29.1%	37.0%		
No	70.9%	63.0%		
Were atypicals being used?			6.93	0.008
Yes	80%	48.1%		
No	20%	51.9%		
Were antianxiety drugs being used			2.20	NS
Yes	41.1%	59.3%		
No	58.2%	40.7%		
Was ECT ever employed			0.02	NS
Yes	23.6%	22.2%		
No	76.4%	77.8%		

<sup>a</sup>Mann-Whitney test; SD, standard deviation; NS, not significant; PANSS, the Positive and Negative Syndrome Scale; HARS, the Hamilton Anxiety Rating Scale; GAF, the Global Assessment of Functioning Scale; ECT, electroconvulsive therapy.

common comorbid anxiety disorders with a lifetime comorbidity of 39.0%, followed by social phobia (13.4%). The prevalence rates determined for OCD and social phobia were in accordance with the results of prior studies. In the literature, comorbidity rates were 7–35%, 8–36% for OCD and social phobia respectively [1,8,17,18]. Braga et al. [1] reported the frequency of comorbid anxiety disorders in patients with schizophrenia as follow: social phobia (17%), OCD (15.1%), GAD (9.4%), anxiety disorder not otherwise specified (7.5%), panic disorder (5.7%), specific phobia (5.7%), PTSD (3.8%), and agoraphobia (1.9%). Cosoff and Hafner [19] reported that the prevalence of social phobia (17%), obsessive-compulsive disorder (13%) and generalized anxiety disorder in schizophrenia were relatively high. On the other hand, there are some studies which have contradictory results. Cassano et al. [20] investigated psychiatric comorbidity in patients with

schizophrenia spectrum disorders and mood spectrum disorders with psychotic features. They found that panic disorder (24%), obsessive-compulsive disorder (24%), social phobia (17.7%), and simple phobia (7.3%) were the most frequent comorbid anxiety disorders. Higher frequency of panic disorder in this study can be explained with the larger and different study group including mood disorders with psychotic features.

High comorbidity rates of OCD and schizophrenia raise the possibility of a common underlying pathology for both disorders. Recent literature suggests some overlap between OCD and schizophrenia on clinical and neurobiological bases, that is, some dysfunction on functional circuits or neurotransmitters systems [21,22]. Some authors argue that schizophrenia with accompanying obsessive-compulsive symptoms constitutes a specific subtype of schizophrenia [23,24].

The experience of paranoia and the social withdrawal found in schizophrenia can mime social anxiety disorder symptoms. Clinical attention needs to focus on the presence of anxiety symptoms associated with avoidance behavior and on the level of insight; both of them are reduced when negative symptoms are predominant in the clinical picture. In schizophrenia, withdrawal behavior linked to negative symptoms is phenomenologically sustained by detachment, while social anxiety is related to interpersonal sensitivity. Although the distinction between social anxiety disorder and negative/positive symptom-related behavior remains somehow difficult, clinical experience shows that this clinical distinction is easier in schizophrenia patients than in patients with a primary diagnosis of social anxiety disorder [8].

In this study, we found that patients with a diagnosis of schizophrenia with comorbid anxiety disorders had shorter duration of illness. However, mean age is significantly lower in the group with comorbid anxiety disorders (31.8 vs. 37.1), and mean age of onset is almost identical between groups (21.5). A lower prevalence of comorbid anxiety disorder in older patients may reflect spontaneous remission with advancing age. Another possible explanation might be that substance use is more common in younger patients with schizophrenia, and an association between anxiety symptoms and anxiety disorders and increased risk of substance use disorders among adults in the general population, as well as in various clinical samples, is well documented [25,26]. Braga et al. [1] did not report a significant relationship between age and the presence of comorbid anxiety disorder in schizophrenia. Goodwin et al. [20] reported no significant differences in age between patients with and without anxiety disorders in a clinical sample. That finding appears to be a matter of course.

Rates of response and remission for anxiety disorders are low despite marked improvements in treatment in the past several decades. Antidepressants and anxiolytics remain the most frequently prescribed agents for anxiety disorders, but the numbers of prescriptions for modern forms of therapy, such as anticonvulsants and atypical antipsychotics are increasing. There are different opinions on the neural basis of the anxiolytic effects of antipsychotics. It has been suggested that typical and atypical antipsychotics could reduce anxiety through direct modulation of the dopamine system [27,28]. For the atypical antipsychotics, agonist activity at the 5-HT<sub>1A</sub> receptor has been hypothesized to translate into anxiolytic effects [29]. A small, but growing literature suggests that atypical antipsychotics are useful as augmentation therapy for treatment of refractory anxiety disorders. Further studies

examining the effect of atypical antipsychotic drugs on anxiety symptoms in patients with schizophrenia are warranted. In our study group, we observed that atypical antipsychotics were more commonly prescribed to patients with a diagnosis of schizophrenia with comorbid anxiety disorders than those without comorbid anxiety disorders. Possibly, atypical antipsychotics were preferred in these patients because of their potential anxiolytic effects. On the other hand, the onset of the illness in patients with comorbid anxiety disorders was on average around 10 years ago while for the patients without comorbid anxiety disorders it was about 16 years ago. Therefore, the difference in prescription of atypical rather than typical antipsychotics between the two groups might simply reflect the increase in the use and availability of atypical antipsychotics over the last 10 to 15 years.

The Hamilton Anxiety Rating Scale did not differ between the two groups and this could be due to the heterogeneity of the anxiety disorders, and to the fact that a general rating scale could not pick up the differences. We did not find a significant difference between two groups with regard to functional disability. Craig et al. [30] found marked temporal instability of the presence of the anxiety symptoms in patients with a diagnosis of schizophrenia over a 2-year follow-up. If most of the anxiety symptoms had not been present for years, it would be unlikely that an effect on disability would be seen. We did not investigate whether the anxiety disorders were currently actively symptomatic or not in our study group. It has been demonstrated that anxiety disorders may impose an additional burden to patients with schizophrenia, resulting in further decline in their subjective quality of life [1,8].

The main limitation of this study lays in the retrospective recall of some variables, which may certainly bias some results. Another limitation is the relatively small sample size that could limit our ability to generalize the results to schizophrenia patients in general. As mentioned above, we did not investigate current status of comorbid anxiety disorders. Anxiety disorders are mainly persistent. Therefore we preferred to evaluate the effects of lifetime comorbid anxiety disorders in patients with schizophrenia. However, it is possible that patients with currently actively symptomatic anxiety disorders may exhibit different clinical features and social functioning. Another limitation of the study is the lack of evaluation of other axis I disorders in these patients.

This study suggests that comorbidity of anxiety disorders is relatively prevalent among outpatients with a diagnosis of schizophrenia. Therefore, special attention to this issue should be paid when

interviewing these patients. Future large-scaled prospective clinical and epidemiological studies are required for a more general view on the subject.

### Key points

- Comorbidity of anxiety disorders is relatively prevalent among patients with a diagnosis of schizophrenia
- Obsessive-compulsive disorder is the most common comorbid anxiety disorder in patients with schizophrenia
- Patients with a diagnosis of schizophrenia with comorbid anxiety disorders had shorter duration of illness than those without such comorbid conditions

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None.

### Statement of Interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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