Relationship between Antidepressant Prescription Rates and Features of Schizophrenic Patients and Its Outcome in Schizophrenia Treatment

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ABSTRACT

Introduction: Comorbid depression in schizophrenia is associated with poor outcome, increased risk of relapse and a high rate of suicide. Identification of depressive symptoms and their appropriate treatment is crucial for depressed schizophrenic patients. The aim of this study is to investigate the rates of antidepressant prescription and their outcomes.

Methods: The records of the schizophrenic outpatients, who were consulted at Psychosis Unit of Psychiatry Department between January 2007 and September 2012, were evaluated retrospectively. Enrolled schizophrenic patients' antidepressant medications were at their minimal effective doses and effective duration.

Results: The present study demonstrates that 39 of the 101 patients during their follow-ups were prescribed antidepressants. The mean follow-up period was 6.3 (± 4.2) years; the mean age at onset was 22 (± 6.5) years; the mean duration of illness was 14.7 (± 7.3) years and the mean number of psychotic exacerbation was 5 (± 3.7). The most prescribed antidepressants

were; sertraline (36.9%), venlafaxine (23.8%) and essitalopram (20.2%). SSRI's were prescribed 57 (73.1%), where as SNRI's 21 times (26.9%). There was no significant difference between SSRI (78.6%) and SNRI (21.4%) treatments in terms of psychotic exacerbation under antidepressant medication. Full remission of depressive symptoms was achieved in 21 patients (53.8%). Remission rates were significantly higher ($p < 0.01$) in SNRI treated depressed schizophrenic patients (85.7%) compared to SSRI treated patients (50.9%). In 8 of the 39 patients (20.5%) antidepressant treatment was terminated due to side effects.

Conclusion: This study demonstrates that SSRI's were more often prescribed compared to other classes of antidepressants in emerging depressive symptoms in schizophrenic patients despite full remission with SNRI's is more common. There was no significant difference between SSRI and SNRI treatment in terms of psychotic exacerbation.

Keywords: Schizophrenia, depression, antidepressant

INTRODUCTION

Depressive symptoms and complaints are frequently seen during the course of schizophrenia (1,2). Studies have shown that the prevalence of depressive symptoms ranges from 20% to 80% in schizophrenic patients (3,4). The reasons of the depressive symptom cluster are not fully explained. Some researchers claim that depressive symptoms are complements to the disorder (5), whereas others claim that antipsychotics lead to these symptoms (6). Many studies have indicated that schizophrenic patients demonstrating depression symptoms are more likely to experience a negative course of the disease, frequent exacerbations and multiple psychotropic drug use, frequent hospitalizations, and frequent early exacerbations (7,8). Comorbid depression in schizophrenia is known to be one of the most important factors to worsen the quality of life (9,10). Additionally, comorbid depression in schizophrenia is known to significantly increase the rate of suicide (11,12,13). In connection with the given outcomes, it is highly important to identify the depressive symptoms in schizophrenic patients as well as their effective treatment.

It is known that 60% of schizophrenic patients experience a major depressive disorder at least once during the course of their illness (14). Antidepressants are frequently used for the treatment of negative symptoms and comorbid depressive symptoms of schizophrenia (15,16). Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies that investigated multiple drug use in schizophrenia patients found that approximately one-third of the patients used antidepressants (17). There are many studies conducted on different types of antidepressants for the treatment of depressive symptoms (18,19,20,21). In addition, to date, there is no study on the frequency of antidepressant use in schizophrenic patients. Thus, the medical records of schizophrenic patients who were followed-up and treated at our clinic were retrospectively evaluated, and the correlation between the frequency of antidepressant use and its characteristics of sociodemography, disease, and treatment was investigated. The current findings were considered to be an inference for appropriate treatment in schizophrenic patients with depressive disorder.

METHODS

In this study, the medical records of patients who were admitted to the Psychosis outpatient clinic between January 2007 and September 2012, who had symptoms for at least 1 year, who were diagnosed with schizophrenia for the first time according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV), or whose previous diagnosis was confirmed and who were treated (medication change, dose adjustment, additional psychiatric medication or first-time antipsychotic medication) were retrospectively evaluated. A special form was filled out for each patient to acquire patient data. With this form, four areas related to the patients were investigated: i) patients' sociodemographic characteristics (sex, age, education level, marital status, employment status, and professional information); ii) disease characteristics (age of onset, frequency of psychotic episodes, frequency of hospitalization, history of suicide attempts, history of electroconvulsive therapy); iii) antidepressant treatment between 2007 and 2012 (year of admittance to the outpatient clinic, type of antidepressant, dose and duration of use, presence of a stressor initiating a depressive episode); iv) treatment course (exacerbation, remission, and side effects during antidepressant use). The present study was approved by the ethics committee.

The basic condition for the patient to be approved for the follow-up in this study was to comply with the date of control set by the doctor (as the patient's follow-up frequency differs according to the patient's condition). However, in cases where the patient did not comply with the follow-up date, the patient was still considered to be included in the follow-up if he/she was known to continue the existing treatment regularly. In cases where hospitalization is required, the patient was considered to be included in the outpatient clinic follow-up if he/she continued to come to the outpatient clinic for follow-ups after being discharged. The patients who had a psychotic disorder depending on the general medical condition or substance use, schizoaffective disorder, axis II disorder, general medical disease, history of substance and alcohol abuse/addiction, and mental deficiency were excluded from the study.

Antidepressants used were separated into three groups: selective serotonin reuptake inhibitor (SSRI) (sertraline, escitalopram, citalopram, fluoxetine, fluvoxamine, and paroxetine), serotonin and noradrenaline reuptake inhibitor (SNRI) (venlafaxine and duloxetine), and other antidepressants (tricyclic antidepressants, bupropion, trazodon ve mirtazapine). All antidepressants were given with efficient dose intervals.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 statistical software. Pearson Chi-square test, Yates-corrected chi-square test, and Fisher's exact chi-square test were used for the evaluation of the categorical data. The significance level was $\alpha=0.05$.

RESULTS

Thirty-nine of 101 patients included in the study were found to have used antidepressants once or more than once. Sociodemographic and disease-related characteristics of the patients are presented in Table 1. Studies revealed that the employment rate of schizophrenic patients using antidepressants was significantly higher than the patients not using antidepressants ($p<0.05$). There was no significant difference between the two groups with regard to sociodemographic characteristics presented in Table 1.

During the follow-ups, it was found that 42.5% of the patients had not used antidepressants. The most commonly used antidepressants were

Table 1. Sociodemographic and clinical features of the patients

		Patients with antidepressant treatment	Patients without antidepressant treatment	Total
Gender	Male	27 (69.2%)	43 (69.4%)	70 (69.3%)
	Female	12 (30.8%)	19 (30.6%)	31 (30.7%)
Marital status	Never married	30 (76.9%)	46 (74.2%)	76 (75.2%)
	Married	8 (20.5%)	10 (16.1%)	18 (17.8%)
	Widow(er)	0 (0.0%)	1 (1.6%)	1 (1.0%)
	Divorced	1 (2.6%)	5 (8.1%)	6 (5.9%)
Educational status	Illiterate	1 (2.6%)	1 (1.6%)	2 (2.0%)
	Literate	1 (2.6%)	3 (4.8%)	4 (4.0%)
	Elementary school	3 (7.7%)	15 (24.2%)	18 (17.8%)
	Pre-high school	11 (28.2%)	8 (12.9%)	19 (18.8%)
	High school	16 (41.0%)	28 (45.2%)	44 (43.6%)
	College/University	7 (17.9%)	7 (11.3%)	14 (13.9%)
Socioeconomic and cultural status	High	0 (0.0%)	5 (8.1%)	5 (5.0%)
	Moderate	30 (76.9%)	42 (67.7%)	72 (71.3%)
	Low	9 (23.1%)	15 (24.2%)	24 (23.8%)
Occupational status	Yes	22 (56.4%)	18 (29.0%)	40 (39.6%)
	No	17 (43.6%)	44 (71.0%)	61 (60.4%)
Current labor status	Working	6 (15.4%)	7 (11.3%)	13 (12.9%)
	Not Working	33 (84.6%)	55 (88.7%)	88 (87.1%)
Living with	Parents and/or siblings	28 (71.8%)	48 (77.4%)	76 (75.2%)
	Spouse or/and children	9 (23.1%)	11 (17.7%)	20 (19.8%)
	Alone	2 (5.1%)	2 (3.2%)	4 (4.0%)
	Other	0 (0.0%)	1 (1.6%)	1 (1.0%)
Family history of the disorder	Yes	5 (12.8%)	6 (9.7%)	11 (10.9%)
	No	34 (87.2%)	56 (90.3%)	90 (89.1%)
History of suicide attempt	Yes	7 (17.9%)	11 (17.7%)	18 (17.8%)
	No	32 (82.1%)	51 (82.3%)	83 (82.2%)
History of convulsive treatment	Yes	3 (7.7%)	5 (8.1%)	8 (7.9%)
	No	36 (92.3%)	57 (91.9%)	93 (92.1%)

sertraline (36.9%), venlafaxine (23.8%), and escitalopram (20.2%). During the use of antidepressants, the patients experienced exacerbation 17 times (20.2%), discontinuation depending on the side effects 16 times (19%), and experienced remission 50 times (59.5%). There were no stressor factors before depressive attack in 89.7% of the patients using antidepressants. The mean length of follow-up in the patients included in the study was 6.3 (± 4.2) years, mean age of onset was 22 (± 6.5) years, mean duration of disease was 14.7 (± 7.3) years, and mean number of psychotic exacerbations was 5 (± 3.7).

Psychotic exacerbation numbers in patients during the use of antidepressants are presented in Table 2. There was no significant difference 65

between antidepressants with respect to psychotic exacerbation during their use. The patients received SSRI 57 times (73.1%), SNRI 21 times (26.9%); they experienced exacerbation 11 times (19.3%) in SSRI and 3 times (14.3%) in SNRI. Exacerbation numbers related to antidepressant use are presented in Table 2. Sertraline, venlafaxine, and escitalopram were the most frequently used antidepressants in the study. There was no statistical comparison among antidepressants because sertraline was the most preferred antidepressant and other depressants were rarely used in patients, although sertraline seems to have the highest exacerbation rate (19.4%) among the antidepressants. The patients received SSRI 57 times (73.1%), SNRI 21 times (26.9%); they experienced exacerbation 11 times (19.3%) in SSRI and 3 times (14.3%) in SNRI. There was no significant difference between the SSRI and SNRI patients ($p=0.748$). The tricyclic antidepressants amitriptyline (75 mg) and clomipramine (150 and 300 mg) were used once, and exacerbation was only observed in a 300 mg dose of clomipramine.

Eight (20.5%) of 39 patients who used antidepressants discontinued drug use depending on side effects; 21 (53.8%) patients were in complete remission with regard to depressive symptoms. The remission rates of depressive symptoms are presented in Table 3. Twenty-nine (50.9%) patients using SSRI and 18 (85.7%) using SNRI were in complete remission with regard to depressive symptoms. The remission rate in patients using SNRI was significantly higher compared with the patients using SSRI ($p<0.01$).

DISCUSSION

The present retrospective study conducted in 101 schizophrenic patients demonstrated that I) the use of antidepressants was 38.6%, II) SSRI group drugs were used more, III) remission in the SNRI group of drugs was more frequent than that in the SSRI group of drugs, and IV) there was no significant difference in exacerbation between the SSRI and SNRI group of drugs.

Given that frequent depressive complaints that accompany schizophrenia affect the course of the disease negatively and that they decrease the life quality which can be achieved through the decrease in these symptoms, it is important to decrease the symptoms at the right time (22). According to previous studies, approximately 38% of the schizophrenic patients who use antipsychotics also use antidepressants (17,23). The 38.6% incidence of antidepressant use in this study is parallel to the literature findings.

An interesting point in this study is that there was no significant difference in the incidence of antidepressant use between genders. Considering the higher incidence of major depressive disorders in females, the insignificant difference in antidepressant medication use between male and female schizophrenic patients may be attributed to the potential etiopathogenic difference between depression in schizophrenia and a major depressive disorder. On the other hand, Chakos et al. (17) reported a higher incidence of antidepressant medication use in female schizophrenic patients compared with male patients.

There are many studies that used all classes of antidepressants to decrease the depressive symptoms accompanying schizophrenia. Amitriptyline (24), imipramine (22), sertraline (19), trazodone (25), reboxetine (26), venlafaxine (21), and milnacipran (20) are some examples. In daily clinical practice, one of the most important topics in the reduction of depressive symptoms accompanying schizophrenia that physicians pay attention to is the exacerbation of psychotic symptoms associated with antidepressant use. Caroli et al. (27) observed a reduction in the depressive symptoms

Table 2. Rates of psychotic exacerbations during antidepressant medication

Antidepressant	Psychotic exacerbations agent		
	Yes	No	Total
Sertraline	6 (19.4%)	25 (80.6%)	31 (100.0%)
Venlafaxine	2 (10.0%)	18 (90.0%)	20 (100.0%)
Escitalopram	2 (11.8%)	15 (88.2%)	17 (100.0%)
Duloxetine	1 (100.0%)	0 (0.00%)	1 (100.0%)
Citalopram	0 (0.00%)	1 (100.0%)	1 (100.0%)
Tricyclic	1 (33.3%)	2 (66.7%)	3 (100.0%)
Trazodone	1 (100.0%)	0 (0.00%)	1 (100.0%)
Fluvoxamine	1 (50.0%)	1 (50.0%)	2 (100.0%)
Fluvoxamine	1 (33.3%)	2 (66.7%)	3 (100.0%)
Bupropion	0 (0.00%)	1 (100.0%)	1 (100.0%)
Paroxetine	1 (33.3%)	2 (66.7%)	3 (100.0%)
Mirtazapine	1 (100.0%)	0 (0.00%)	1 (100.0%)
Total	17 (20.2%)	67 (79.8%)	84 (100.0%)

Table 3. Rates of remission under antidepressant medication

	Remission		Total
	Achieved	Not Achieved	
SSRI	29 (50.9%)	28 (49.1%)	57 (100.0%)
SNRI	18 (85.7%)	3 (14.3%)	21 (100.0%)
Total	47 (60.3%)	31 (39.7%)	78 (100.0%)

SSRI: selective serotonin reuptake inhibitor; SNRI: selective serotonin-noradrenaline reuptake inhibitor

in the psychotic symptoms. Mulholland et al. (19) did not observe an exacerbation in psychotic symptoms with sertraline use in a double-blind, placebo-controlled study. Kırılı et al. (22) treated two groups consisting of 20 patients with schizophrenia with a constant dose of sertraline (50 mg/day) and imipramine (150 mg/day) and monitored the patients for 5 weeks. It was reported that there was an exacerbation in the psychotic symptoms in two patients in the imipramine group, whereas there was no exacerbation in the sertraline group. In the double-blind, placebo-controlled study by Addington et al. (28), there was no significant difference in the depressive symptoms between the sertraline and placebo groups. According to the results of this study, the incidence of exacerbation and remission in patients who used sertraline is 19.4% and 51.6%, respectively. In the randomized, double-blind, placebo-controlled study by Iancu et al. (29), there is no significant difference in the reduction of intensity of the depressive symptoms between the escitalopram and placebo groups, whereas exacerbation of psychotic symptoms was observed in 2 out of 19 patients at the end of week 8. The incidence of exacerbation because of escitalopram given to the patients in this study was found to be similar with the study of Iancu et al. (29). The present data regarding the incidence of exacerbation are very similar to the findings of this study.

In the study by Danaci and Aydemir (21), eight patients with depressive symptoms accompanying schizophrenia were monitored with venlafaxine, and there was a significant reduction in depressive symptoms, whereas there was no exacerbation in the psychotic symptoms. A 150

mg/day dose was used in 2 out of 8 patients, and a 75 mg/day dose was used in the remaining patients. Similarly, Mazeh et al. (18) reported that there was a significant reduction in the depressive symptoms accompanying schizophrenia in 19 patients with schizophrenia who received venlafaxine treatment on an average dose of 146 mg/day (75–225 mg/day), and there was no exacerbation of psychotic symptoms. Similarly, there was a significant reduction in depressive symptoms in a study that used the double-effective antidepressant milnacipran, and there was no exacerbation of the psychotic symptoms in any patient (20). When the findings of this study were examined, venlafaxine treatment was preferred 20 times, but was used in 150 mg/day dose in four cases and 75 mg/day in the remaining cases. Remission was observed in 17 patients, and exacerbation of psychotic symptoms was observed in two patients.

It was observed that the number of studies that compared antidepressant treatments in schizophrenia is low in our country, and in other countries, placebo-controlled studies are generally conducted and that there is no study that compares SNGI and SSGI treatments. On the other hand, according to a literature search, there is no retrospective study that investigated the use and results of antidepressants to decrease depressive symptoms accompanying schizophrenia. It is believed that monitoring of patients in a special unit by the same physician during data evaluation and a mean follow-up period of 6 years constituted the advantages of the study in terms of monitoring depressive symptoms, reducing the symptoms, and evaluating the results. On the other hand, the retrospective nature of the study was the major limitation of this study. Given the retrospective nature of this study and the fact that it was based on clinical observations, it is unclear whether the observed exacerbation of psychotic symptoms were related to the course of schizophrenia or the use of antidepressants.

In conclusion, comorbid depression in schizophrenia and its negative effects on the disease are widely known today. Therefore, the determination of depressive symptoms and appropriate treatment options are required for the appropriate treatment of depressive symptoms and complaints in schizophrenic patients. To further understand this delicate point, there is a need for more systematic, more comprehensive in terms of patient number, double-blind, placebo-controlled studies that investigate long-term data regarding the use of antidepressants, which are used to decrease the depressive symptoms accompanying schizophrenia.

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