

Comparison of Sexual Function and Hormonal Parameters Between Mood Stabilizer Treatment Modalities in Bipolar Disorder

İki Uçlu Bozuklukta Duygudurum Düzenleyici Tedavi Modaliteleri Arasında Cinsel İşlev ve Hormonal Değişkenlerin Karşılaştırılması

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ABSTRACT

Introduction: The aim of this study was to determine the differences between lithium and atypical antipsychotics (quetiapine and olanzapine) with regard to their effects on sexual functions and hormonal variables and to assess the findings in term of gender differences, in patients with bipolar disorder.

Method: 28 female and 29 male patients diagnosed as having bipolar disorder type I according to the DSM-IV, using lithium or quetiapine and quetiapine+lithium or olanzapine and olanzapine+lithium were evaluated consecutively. Being in remission period and given informed consent were set as inclusion criteria in these cases. Interviews with the patients were carried out using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and SKIP-TURK. Sexual functions and satisfaction were evaluated with the Arizona Sexual Experiences Scale (ASEX) and the Golombok Rust Inventory of Sexual Satisfaction (GRISS). Blood samples of the patients were taken in order to determine prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and free testosterone (T) levels.

Results: GRISS scores in male patients were higher than in female patients ($p=.001$). The number of manic, depressive and total episodes, and functionality levels were similar between the treatment groups, both in female and male patients. No differences were found between treatment modalities in terms of hormone levels both in female and male patients. Among females, ASEX scores of the patients treated with lithium monotherapy were less than the ones treated with quetiapine and olanzapine. Among patients with quetiapine monotherapy, GRISS scores in male patients were higher than in female patients.

Conclusion: There are some evidences showing gender-based differences in the side effects of atypical antipsychotic drugs. Future studies with a specific focus on this topic are needed in order to have a better understanding of the basic mechanisms of gender differences. (*Archives of Neuropsychiatry 2014; 51: 242-247*)

Key words: Gender, sexual side effect, psychotropics, bipolar disorder

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ÖZET

Giriş: Bu çalışmanın amacı, İUB tanılı olgularda, atipik antipsikotiklerin (ketiyapin ve olanzapin) cinsel işlev ve hormonal değişkenler üzerine etkisinin lityumdan farklı olup olmadığını ve bu etkinin cinsiyetler arasında farklılaşp farklılaşmadığını incelemektir.

Yöntem: DSM-IV'e göre iki uçlu bozukluk tanılı, lityum, ketiyapin ya da lityum+ketiapin, olanzapin ya da lityum+olanzapin kullanan, 28 kadın, 29 erkek olgu, ardışık olarak değerlendirildi. Bu olgularda iyilik döneminde olma ve bilgilendirilmiş onam şartı arandı. Hasta görüşmeleri SCID-I ve SKIP-TURK ile yapıldı. Cinsel işlev ve doyum Arizona Cinsel Deneyim Envanteri (ASEX) ve Golombok-Rust Cinsel Doyum Envanteri (GRISS) ile değerlendirildi. Prolaktin (PRL), folikül uyarıcı hormon (FSH), luteinize edici hormon (LH), östradiol (E2) ve testosteron (T) düzeyleri bakılmak üzere hastalardan kan örnekleri alındı.

Bulgular: Erkek iki uçlu olguların GRISS puanları kadın iki uçlu olgulardan yüksekti ($p=.001$). Hem kadın hem erkek olgularda epizod sayısı ve işlevsellik düzeyi her üç tedavi grubunda benzerdir. Hormonal değişimler yönünden hem kadın hem erkek olgularda tedavi tipleri arasında bir fark saptanmadı. Sadece lityum alan kadınlarda ASEX puanları, ketiyapin ve olanzapin alan kadınlardan daha düşük bulunurken, ketiyapin alan erkeklerin GRISS puanları, ketiyapin alan kadınlardan daha yüksek bulundu.

Sonuç: Atipik antipsikotik ilaçların yan etkilerinde cinsiyet farklılıkları olabileceğine ilişkin bazı kanıtlar vardır. Cinsiyet farklılıkları ile ilgili temel mekanizmaların daha iyi anlaşılması için, bu konunun üzerine bir odak noktası ile gelecek çalışmalara ihtiyaç vardır, daha özgül veriler bu farklılıkların klinik etkilerini anlamaya yardımcı olacaktır. (*Nöropsikiyatri Arşivi 2014; 51: 242-247*)

Anahtar kelimeler: Cinsiyet, cinsel yan etki, psikotropikler, iki uçlu bozukluk

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Side effects, including sexual dysfunction (SD), that disturb treatment compliance have been reported with a rate ranging between 18% and 96% with atypical antipsychotics (1). When the literature is examined, it is observed that sexual dysfunction most frequently occurs with risperidone and least commonly with quetiapine in many studies (2,3,4,5,6,7,8,9,10). In a study in which quetiapine was not included, no significant difference was found in terms of SD in patients who were receiving risperidone, olanzapine, haloperidole, and aripiprazole monotherapy (11). In an animal study, sexual function was suppressed in a dose-dependent fashion when risperidone was chronically administered to healthy horses, whereas sexual behavior was not observed to change with quetiapine (12). In a recent meta-analysis, quetiapine, ziprasidone, and aripiprazole were found to be associated with SD with a relatively low rate (16%–27%), whereas risperidone, olanzapine, and clozapine were associated with SD with a higher rate (40%–60%) (13). In this meta-analysis, SD was defined as disruptions in sexual drive, arousal, and orgasm. While dopaminergic disorder is directly related with disruptions in sexual drive and orgasm, blocking or regulatory mechanisms of serotonin, adrenaline, histamine, and acetylcholine may lead to secondary sexual problems. Secondary hyperprolactinemia is frequently dose dependent and its relationship with SD is considered to be more prominent in women than in men (14). SD is reported with a higher rate in men and is more frequently observed in association with treatment noncompliance (15). Gender differences may also be present in sexual side effects of mood stabilizer treatment modalities.

At this point, it should be noted that all the studies mentioned above in relation with SD caused by atypical antipsychotics were conducted with patients diagnosed with schizophrenia and schizoaffective disorder. Studies conducted with patients diagnosed with BD in this area are limited with lithium. In 1992, Ghardian et al. (16) reported that the use of lithium alone did not cause SD in patients with a diagnosis of BD. In 1996, Aisenberg et al. (17) revealed that lithium levels were similar in patients having BD with and without SD. In the same study, it was reported that SD that frequently occurred as disruption in sexual desire and arousal was mostly observed in male patients.

Another issue we consider is the fact that the effect of the disease itself on SD was not considered in these studies. Thus, only 30% of patients with BD who received long-term lithium treatment attributed present SD to lithium (18). In a study in which the first-episode patients with psychosis were evaluated in the subsequent

remission period, SD was found with a rate of 45% (19). In addition, no difference was found between patients with and without SD in terms of medication, prolactin (PRL), and E levels.

Objective

This study aimed to compare the effects of atypical antipsychotics (quetiapine and olanzapine) on sexual function and hormonal variables with lithium in patients with a diagnosis of BD. Secondly, it was aimed to examine if this effect was different between genders.

Methods

Sample and Application

Our study is a naturalistic and cross-sectional study. With this objective, we consecutively evaluated patients who accepted to participate in the study by signing the informed consent form among the subjects who presented to outpatient clinic with a diagnosis of BD in accordance with DSM-IV who were in remission for at least 4 weeks and who were using lithium, quetiapine, olanzapine, lithium plus quetiapine, and lithium plus olanzapine (Table 1). Furthermore, the addition of subjects who were using quetiapine+lithium and olanzapine+lithium to subjects who were using quetiapine and olanzapine was preferred to increase the number of subjects. Additionally, it was considered that the use of lithium would not affect the difference of sexual function (if present) in comparisons with lithium alone. The subjects who had a co-diagnosis of alcohol and substance abuse and any medical condition requiring treatment were excluded from this study.

The reason that quetiapine and olanzapine were selected among atypical antipsychotics was because these two drugs were being most commonly used in bipolar disorder and their mood stabilizing properties had been clearly demonstrated (20). In addition, it was considered that the findings related with sexual function could be interpreted independent of prolactin level because these drugs affected prolactin level relatively less. A side effect of lithium as sexual dysfunction has not been clearly demonstrated till date (20). Moreover, it is known that it does not cause a change in gonadal hormones. Therefore, patients with BD using lithium were selected as the control group.

SKIP-TURK Mood Disorder Diagnosis and Follow-up Form was filled in the following diagnostic interviews with patients having BD and using SCID-I (21). Subsequently, blood samples

Table 1 . Sample

| | BD patients using lithium (s=18) | BD patients using quetiapine or quetiapine +lithium (s=18) | BD patients using olanzapine or olanzapine +lithium (s=21) |
|---------------|---|---|---|
| Female (s=28) | 6 | 12 | 10 |
| Male (s=29) | 12 | 6 | 11 |

were obtained from all patients to measure PRL, FSH, LH, E2, and T levels. Approval was obtained from the Education Planning Committee of Erenköy Psychiatry Education and Research Hospital for the study, and the cost of blood tests was covered by the Hospital Research Budget Fund.

Tools

SKIP-TURK Mood Disorder Diagnosis and Follow-up Form

This form examines the age at onset of disease, age at onset of treatment, history of physical and sexual abuse, history of physical illness, academic and social functionality, premenstrual syndrome, history of smoking, history of alcohol, and substance abuse; type of the first episode, stressor before the episode, episode severity, onset after delivery, depression subtype, episode with psychotic symptoms, suicide attempt, hospitalization, episode time, and how it was alleviated; and number of episodes in total before and after prophylactic treatment and for each period, stressor before episode, episode severity, episode time, episode with psychotic symptoms, suicide attempt, hospitalization, dominant course pattern, seasonality, acute onset and remission, chronicity, and rapid cycling, switching, and if full recovery occurred (22).

Hamilton Depression Rating Scale

The Turkish validity and reliability study of this scale that measures the severity of depression was performed by Akdemir et al. (23).

Young Mania Rating Scale

This scale that is used to determine the severity of manic symptoms was developed in 1979 by Young et al. Its Turkish validity and reliability study was performed by Karadağ et al. (24).

Arizona Sexual Experiences Scale (ASEX)

This scale comprises five items and aims to determine sexual drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. The possible total score ranges between 5 and 30, and as the score gets higher, the severity of sexual dysfunction increases (25). This scale was tested in patients with a diagnosis of schizophrenia and schizoaffective disorder and was accepted as a tool with a high specificity and sensitivity (4). The validity and reliability study of this scale for our country was performed by Soykan et al. in 2004 (26).

Golombok Rust Satisfaction Scale (GRISS)

The validity and reliability study of this scale that aimed at determining the disturbance in sexual drive, sexual satisfaction and sexual function in our country was performed by Tuğrul et al. in 1993 (27,28). The scale is composed of 28 items. In the female form, the total score as well as the scores of the subscales, including anorgasmia, vaginismus, communication, frequency, avoidance, and satisfaction, is calculated. In the male form, the scores of the subscales, including impotence, premature ejaculation, ill-communication, frequency, avoidance, and dissatisfaction, are calculated in addition to the total score. This scale is generally used in studies that are conducted to examine

the effects of pharmacology on sexual functions. As the score gets higher, the severity of sexual dysfunction increases.

Statistical Analysis

The t-test was used in paired comparisons (SD/mean<.3). Analysis of variance was used for comparison of the groups. Bonferroni correction was used in the post-hoc analyses. A p value of <.05 was considered statistically significant. All tests were two-tailed tests.

Results

Description of the sample

The mean age; mean age at onset of BD; number of manic, depressive, and total episodes; and level of functionality were similar in the female and male subjects with BD. Furthermore, no difference was found between lithium, quetiapine, and olanzapine groups in terms of the mean age; mean age at onset of BD; number of manic, depressive, and total episodes; and level of functionality (Table 2). In contrast, the mean age and age at onset of BD were found to be younger in the olanzapine group in male subjects 4 (Table 3).

Comparison of female and male subjects with BD in terms of sexual function

When all female subjects with BD were compared with all male subjects with BD independent of treatment type, ASEX scores were found to be similar, whereas GRISS scores were found to be higher in male subjects than in female subjects ($t=2.2$, $p=.001$).

When female subjects in each treatment type were compared with male subjects in the same treatment type, GRISS scores of male subjects who were using quetiapine or quetiapine+lithium were found to be higher than in female subjects who were using quetiapine or quetiapine+lithium ($t=1.8$, $p=.046$).

Comparison of treatment types in female subjects in terms of sexual function and hormonal variables

PRL, FSH, LH, E2, and free T levels were similar and in the normal range for all treatment types (Table 4). ASEX scores were found to be lower in female subjects who were using only lithium compared with female subjects who were using quetiapine and olanzapine ($F=2.456$, $p=.056$), (Table 4). GRISS scores of female subjects with BD were not found to be different for the three treatment types.

Comparison of treatment types in male subjects in terms of sexual function and hormonal variables

PRL, FSH, LH, E2, and free T levels were similar and in the normal range in all treatment types (Table 5). ASEX and GRISS scores of male subjects with BD were not found to be different for the three treatment types.

Discussion

This is the first study examining the effect of different treatment types on sexual function in patients with BD in company with hormonal variables. Another characteristic of our study that we considered significant is the fact that the clinical course

characteristics of subjects were similar in all three treatment types. This means that the effect of the disease itself on SD was similar in each of the three groups; thus, SD arising from medication can be assumed to be more comparable.

While ASEX scores of female and male subjects with BD were similar, GRISS scores of male subjects were calculated to be higher. When the types of mood stabilizer treatment were separately evaluated, GRISS scores of female subjects who

Table 2. Clinical characteristics in female BD patients

| | Lithium n=6 | Quetiapine or quetiapine +lithium n=12 | Olanzapine or olanzapine +lithium n=10 | Analysis | |
|---|----------------|---|---|----------|------|
| | | | | f | p |
| Age | 31.4±2.1 | 36.2±4.1 | 34.3±8.5 | .130 | .780 |
| Age of onset of BD | 23.7±2.6 | 25.5±3.4 | 24.3±3.2 | .148 | .766 |
| Total episode number | 4.9±1.3 | 3.5±.7 | 4.3±1.5 | .242 | .790 |
| Number of manic episodes | .8±.5 | 3.1±1.7 | 2.3±1.1 | .765 | .491 |
| Number of depressive episodes | 4.2±.7 | 1.3±.6 | 2.2±.5 | .398 | .682 |
| General assessment of functionality (GAF) | 70 | 77.5±3.5 | 75±5 | .510 | .609 |

Table 3. Clinical characteristics in male BD patients

| | Lithium n=6 | Quetiapine or quetiapine +lithium n=12 | Olanzapine or olanzapine +lithium n=10 | Analysis | |
|---|----------------|---|---|----------|------|
| | | | | f | p |
| Age | 42.4±8.2 | 42.8±13.2 | 32.4±6.9 | 4.213 | .024 |
| Age of onset of BD | 32.6±13.1 | 38.5±12.1 | 22.5±5.9 | 8.692 | .001 |
| Total episode number | 4.2±2.1 | 2.5±1.1 | 5.4±1.4 | .463 | .634 |
| Number of manic episodes | 3.2±1.5 | 1.2±.5 | 4.6±1.6 | .258 | .775 |
| Number of depressive episodes | .8±.5 | 1.5±.8 | .7±.2 | 2.927 | .072 |
| General assessment of functionality (GAF) | 94.6±8.7 | 68.1±13.8 | 78.2±18.2 | .874 | .113 |

Table 4. Sexual function scores and hormonal variables in the female BD patients

| | Lithium n=6 | Quetiapine or quetiapine +lithium n=12 | Olanzapine or olanzapine +lithium n=10 | Analysis | |
|-------|----------------|---|---|----------|------|
| | | | | f | p |
| ASEX | 9.2±1.7 | 18.5±4.9 | 15.3±6.5 | 2.456 | .056 |
| GRISS | 43.8±3.6 | 32.2±12.7 | 35.7±11.1 | 1.997 | .175 |
| PRL | 14.5±3.3 | 19.5±9.6 | 20.6±5.2 | 2.234 | .102 |
| FSH | 9.3±1.2 | 6.4±1.1 | 7.3±1.8 | 2.245 | .109 |
| LH | 8.1±1.3 | 6.7±.5 | 7.1±.8 | 2.234 | .107 |
| E2 | 42.8±12.2 | 78.5±27.5 | 59.9±26.4 | 1.279 | .345 |
| fT | .9±.2 | 1.7±.8 | 1.4±.7 | .681 | .526 |

Table 5. Sexual function scores and hormonal variables in the male BD patients

| | Lithium n=6 | Quetiapine or quetiapine +lithium n=12 | Olanzapine or olanzapine +lithium n=10 | Analysis | |
|-------|----------------|---|---|----------|------|
| | | | | f | p |
| ASEX | 11.2±2.8 | 15.3±6.1 | 11.6±5.8 | 1.844 | .176 |
| GRISS | 72.6±13.6 | 87.3±26.2 | 84.2±18.3 | .831 | .448 |
| PRL | 15.8±4.7 | 19.2±8.3 | 21.6±3.2 | 1.234 | .122 |
| FSH | 5.1±1.4 | 3.1±1.3 | 2.1±1 | 3.987 | .112 |
| LH | 7.2±.9 | 8.2±1.3 | 5.3±.7 | 4.448 | .318 |
| E2 | 61.1±18.2 | 56.8±9.1 | 41.9±16.7 | .202 | .844 |
| fT | 4.3±21 | 4.9±2.2 | 8.1±6.1 | .611 | .567 |

were using quetiapine were found to be higher compared with female subjects who were using quetiapine. These findings can be interpreted such that male patients with BD are affected by the side effects of the psychopharmacological treatment related with sexual function with a higher rate in accordance with the findings related with patients with schizophrenia and schizoaffective disorder in the literature. As a matter of fact, the information that women are affected by the side effects of psychopharmacological treatment related with sexual function with a higher rate was mostly obtained from studies in which hyperprolactinemia was not controlled (14). In our subjects, no difference was found in terms of PRL levels, and PRL levels were within the normal limits. Differences of expectations from sexuality between men and women and psychosocial factors, including cultural characteristics (learned behavior), are considered to have contributed to these findings. In addition, it should not be ignored that male patients may state complaints of sexual dysfunction with a higher rate because erectile dysfunction arising from the effects of medication indirectly results in loss of sexual drive and brings along difficulty in orgasm. In the study of Hariri et al. conducted in 2009, male patients with BD had higher scores in terms of SD and had more information and sought assistance with a higher rate in relation with the side effect of SD (29).

The clinical picture related with the side effects of psychotropic drugs may be different between genders (30). In the study of Aisenberg et al. related with lithium conducted in patients with BD, SD that was observed in the form of disruption in sexual drive and arousal was reported to frequently occur in male subjects (17). The difference between genders was reported to include side effects related with weight gain and metabolic syndrome related with antipsychotic medication, cardiac arrhythmia, and sexual dysfunction (14). In many situations, differences that appeared to be related with gender were found to be related with other factors affecting the side effects, including age, morbidity, and body weight (30). The pharmacokinetics and pharmacodynamics of antipsychotic drugs are different in men and women and are affected by other factors, including body structure, diet, smoking, simultaneous medications, exercise, substance use, and hormonal status. With respect to pharmacokinetics, the plasma blood level has been found to be higher in women than in men only for olanzapine and clozapine. In contrast, changes in prolactin levels and plasma homovalinic acid levels have been found to be higher in women receiving antipsychotic drugs than in men receiving antipsychotic drugs.

Prolactin has a key significance in sexual dysfunction occurring with antipsychotics (31). It has been stated that hyperprolactinemia may be one of the mechanisms responsible for sexual dysfunction, and a decrease in gonadal hormones may decrease libido in both genders. It has been reported that sertindol, quetiapine, ziprasidone, aripiprazole, olanzapine, and clozapine, which are atypical antipsychotics, have no significant effect on prolactin levels. Prolactin levels transiently increase and in a dose-dependent fashion in patients using olanzapine, whereas no increase occurs with quetiapine after the initial dose (32).

In our study, the levels of pituitary and gonadal hormones did not reveal a difference in male and female subjects with BD in all three treatment types and were found to be within the normal range. Similarly, PRL levels did not demonstrate a difference in both genders and in all three treatment types. We believe that this is a significant advantage in terms of interpreting SD independently from PRL level. Thus, sexual function and satisfaction evaluated with ASEX and GRISS did not demonstrate a difference in the three treatment modalities in male subjects in company with similar PRL levels. In contrast, sexual function evaluated by ASEX appeared to be better in female patients with BD who were using only lithium compared with the ones who were using quetiapine and olanzapine. A similar condition was not observed in the male subjects. In relation with this, Aisenberg et al. reported that SD that frequently occurred as disruption in sexual desire and arousal in patients with BD using lithium was mostly observed in male patients in the study they conducted in 1996 (17).

Among male patients with BD, GRISS scores that were different compared with female subjects were observed in male subjects who were using quetiapine or quetiapine+lithium. No gender difference was observed in subjects who were using lithium and olanzapine or olanzapine+lithium. However, it has been reported that sexual dysfunction most commonly occurs with risperidone and least commonly with quetiapine in the literature (2,3,4,5,6,7,8,9,10). The studies that have found quetiapine or olanzapine to be superior in terms of SD caused by medication are found together in the literature (7,32). Similar to our study, Kelly and Conley compared fluphenazine, risperidone, and quetiapine in a 12-week double-blind, randomized study and found that quetiapine (50%) caused to sexual dysfunction with a lower rate compared with fluphenazine (78%) but with a higher rate compared with risperidone (42%) (4). Another interesting finding of the same study was the fact that risperidone that caused hyperprolactinemia was demonstrated to cause sexual dysfunction with a lower rate compared with quetiapine that was not found to lead to an increase in PRL. This was considered as an indicator of the fact that increased PRL by itself was not responsible of sexual dysfunction. In a recent meta-analysis, association of olanzapine with SD with a high rate (40%–60%) was also emphasized (13). A reason of the fact that SD was not found to be worse in the subjects who were using olanzapine in our study may be that female and male subjects were separately evaluated. Another reason may be the fact that the mean age of our male subjects who were using olanzapine or olanzapine+lithium were younger, although the disease times were similar to the other treatment groups. Similarly, the reason that GRISS scores that were different compared with female subjects were observed in male subjects who were using quetiapine or quetiapine+lithium may be the fact that these individuals were older and had a higher number of depressive episodes and lower functionality scores, though insignificantly.

The most important limitation of this study is the low number of subjects in each treatment type. At this point, we can mention

the low number of patients who were being followed up with monotherapy. The second and more important limitation is a lack of a healthy control group. In contrast, SD was found with a considerably higher rate in healthy individuals in the only study in which a healthy control group was included (19). Thus, a lack of difference compared with healthy individuals will not mean that SD is not a problem in these patients.

There is some evidence that gender difference may be present in the side effects of antipsychotic drugs. Studies that will focus on this issue are required to elucidate the main mechanisms related with gender differences. Specific data related with the issue will help us to understand the clinical effects of gender difference.

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