Comparative study of sexual dysfunction and serum prolactin level associated with olanzapine, risperidone, and clozapine in patients with remitted schizophrenia

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ABSTRACT

Background: Sexual dysfunctions have been a major side effect of the second generation anti-psychotic drugs which often affects treatment compliance in patients with schizophrenia. There is no/few systematic review or research addressing sexual dysfunction and their effect on serum prolactin level among different atypical antipsychotics in India.

Aims: To determine and compare the frequency of sexual dysfunction associated with olanzapine, risperidone, and clozapine and their effect on serum prolactin level in remitted patients with schizophrenia.

Settings and Design: Cross-sectional hospital-based study. Recruitment by purposive sampling. Estimation of serum prolactin was done using enzyme-linked immunosorbent assay technique.

Materials and Methods: The total sample size was 103, consisting of 31, 23, and 19 patients in olanzapine, risperidone, and clozapine groups, respectively and 30 controls. A Brief Psychiatric Rating Scale, Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale and Sexual Functioning Questionnaire were administered. Analysis of variance was used to compare clinical variables. Chi-square test was used to identify the frequency of sexual dysfunction. Kruskal–Wallis test was used to compare UKU side effect, sexual dysfunction, and blood parameters across the study groups.

Results and Conclusion: Eighty-six percentage reported sexual dysfunction in one or more domains of sexual functioning in risperidone group as compared to 48.3% in olanzapine and 31% in clozapine groups, respectively. Prolactin level elevation was statistically significant in risperidone group followed by clozapine and olanzapine groups, respectively.

Key words: Clozapine, olanzapine, risperidone, schizophrenia, sexual dysfunction

INTRODUCTION

Sexuality has been a consistent focus of curiosity, interest, and analysis to human being. Sexual function is the physiological capacity to experience desire, arousal, and orgasm. Sexual function involves complex interactions between the nervous system, endocrine system, vascular system, and various psychological factors important for sexual arousal, intercourse, and satisfaction. Sexual
dysfunction can be symptomatic of biological problems, intrapsychic conflicts, interpersonal difficulties, cultural influences, or a combination of these factors. It is either way true that people with sexual problems have a greater chance of various psychiatric illnesses and in patients with psychiatric illness, sexual dysfunction can be one of the clinical manifestations.

The second generation antipsychotic drugs have a greater affinity for serotonin 5-HT$_2$ receptors than for D2 receptors that account for the reduced incidence of sexual side effects.$^{[2,3]}$ However, studies comparing the effect of typical and atypical antipsychotics on sexual functions are few, and those too do not report any significant difference in sexual dysfunction.$^{[4,5]}$ Few of the Indian studies tried to address sexual dysfunction associated with antipsychotic use, however, biological parameter like serum prolactin levels was not included in them.$^{[6-8]}$ In our study, we tried to overcome the limitations of previous studies by including larger number of sample size, included normal controls to take cut-off value to define sexual dysfunction and most importantly serum prolactin level was included as biological parameter.

**MATERIALS AND METHODS**

The study was a cross-sectional, hospital-based study in which subjects were included using the purposive sampling method. After obtaining approval from the Institutional Ethical Committee, patients with diagnosis of schizophrenia as per the International Classification of Diseases, Revision-10 (Diagnostic Criteria for Research) stabilized on either olanzapine, risperidone or clozapine for at least 6-month and in remission, visiting Outpatient Department of the Central Institute of Psychiatry during June 2010 to February 2011 were recruited for the study. Healthy controls were chosen from the relatives of patients or hospital staff. Only those sexually active married male subjects between 18 and 50 years of age without any comorbid psychiatric disorders or substance abuse willing to give written informed consent were included. Those who had significant neurological or medical illness such as diabetes mellitus, cardiovascular disease, endocrine disorder, gonadal injury, or on any medications known to cause sexual dysfunction were excluded from the study. Finally, four groups comprising of 31 patients on olanzapine, 23 on risperidone, 19 on clozapine, and 30 healthy controls were incorporated.

Also specially designed sociodemographic and clinical data sheet were used to record the demographic and clinical variables. A detailed treatment history was obtained including present medications (for last 6 months) and past medications from the file review with respect to dose, type, compliance, and side effects were recorded. The only allowed medication along with the above-mentioned antipsychotics was trihexyphenidyl (THP), given to control extrapyramidal side effects associated with antipsychotic use.

Following this, a detailed physical examination which includes height in centimeters, weight in a kilogram, pulse rate, blood pressure in right arm in supine position, and other systemic examination was done. Then patients were evaluated on the Brief Psychiatric Rating Scale (BPRS)$^{[9]}$ and healthy controls on General Health Questionnaire-12 (GHQ-12). Remission in schizophrenia was defined by a score of <4 on all items of BPRS.$^{[10]}$ GHQ-12$^{[11]}$ of <3 was used for defining healthy controls. Single symptom domain of Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale$^{[12]}$ was applied to the three patient groups and sexual functioning questionnaire (SFQ)$^{[13]}$ on all the study subjects.

Blood samples were collected between 9 am and 4 pm$^{[14]}$ for the estimation of serum prolactin level by enzyme-linked immunosorbent assay method and also for the measurement of random blood sugar (RBS), lipid profile, blood urea, serum creatinine, and thyroid profile to evaluate for some other common causes of sexual dysfunction. A cut-off of 11.94 ng/ml (as provided by the equipment manufacturer) was used for defining hyperprolactinemia.

The BPRS consists of 19 somewhat global, clinically familiar symptoms, and behavior constructs that span much of the range to manifest psychopathology. The UKU side effect rating scale is an observer rated scale and the total UKU scale contains three parts: (1) Single symptom rating scale, (2) scale for global assessment, and (3) scale for stating consequences of the side effects. The reliability of the scale ranges from 0.3 to 0.9. We used only the single symptom rating scale part of the UKU and rated on 0–3 Likert scale. It consists of four subscales viz., psychic, neurological, autonomic, and others (which also includes items for sexual side effects).

The SFQ was the modified version of a questionnaire used by Burke et al.$^{[15]}$ For those who did not know English, a vernacular translation was administered by the author. The SFQ asked detailed questions about the physical aspects of sexual functioning including libido, physical arousal, masturbation, orgasm (including painful orgasm) and ejaculation. The scale, though not tested adequately for validity, had good reliability: Cronbach’s $\alpha$ =0.90; Guttman’s split-half reliability = 0.86. For the purpose of statistical analysis, an arbitrary cut-off point of one standard deviation (SD) above the mean was taken as the threshold above which sexual dysfunction was said to be present. Taking that, subscales of the questionnaire served as continuous variables, which were studied across the study groups. The data from healthy volunteers was collected for statistical purposes, to set a normal mean score on SFQ.
Statistical analysis
The statistical analysis of data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 16.0. Chicago, SPSS Inc.) and Microsoft Excel (Redmond, Washington: Microsoft, 2003. Computer Software).

Descriptive statistics was used to define the sample characteristics. Comparison of sociodemographic variable and the frequency of sexual dysfunction across the study groups were done using the Chi-square test, with Fischer’s exact wherever the cell counts were <5. Analysis of variance was used to compare the sample characteristics of clinical variables.

One sample Kolmogorov–Smirnov (KS) test was done to test the normality of the distribution. As the distribution was not normally distributed, nonparametric comparative statistics was used to compare UKU side effect and blood parameters across the study groups using the Chi-square test for bivariate variables (presence/absence of side effects) and Kruskal–Wallis test for continuous variables (severity of the side effects).

RESULTS

Sociodemographic and clinical characteristics of the subjects were assessed using descriptive statistics [Tables 1 and 2]. No significant difference was noted on comparison among the three patients group. Each of the patient groups were also comparable with normal controls in sociodemographic and clinical variables, except for that olanzapine group was represented by higher number of tribals (of ethnicity) ($X^2 = 8.63, P = 0.047$) and farmers (as occupation) ($X^2 = 5.93, P = 0.021$) in comparison to normal controls. Eight-seven percentage of the patients in risperidone group were also receiving THP that was much higher ($F = 16.4, P < 0.01$) than olanzapine and clozapine groups.

One sample K-S test was done to test the normality of the distribution of scores rated on UKU side effect. As the distribution was not normally distributed, nonparametric Chi-square test was used to compare the presence of side effects of antipsychotics [Table 3]. Significantly higher number of patients in risperidone group suffered from neurological (tremors, rigidity, and hypokinesia) and other side effects (which includes the sexual side effects), whereas those in the clozapine group had more frequent autonomic side effects (hypersalivation, constipation, orthostatic hypotension, and palpitations). Severity as compared using Kruskal–Wallis test also showed higher severity of neurological ($X^2 = 18.868, P < 0.001$) and others ($X^2 = 16.54, P < 0.001$) UKU side effects by risperidone group and severe autonomic side effects by clozapine group ($X^2 = 65.311, P < 0.001$) in comparison to other two groups, respectively.

To analyze the sexual dysfunction, the mean scores of the SFQ on the domains of desire, arousal, erection, masturbatory guilt, and ejaculation/ orgasm were obtained. The SFQ is designed as such that the higher the score, more severe is the sexual dysfunction. An arbitrary cut-off point of one SD above the mean score of healthy volunteers was taken as the threshold above which sexual dysfunction was said to be present. The mean scores on all the domains were compared across the study groups using the Chi-square test, as proportions and level of significance were calculated from this Chi-square test was used to identify the frequency of sexual dysfunction across three groups.

Of 23 patients, 20 (86%) reported sexual dysfunction in risperidone group as compared to 58.3% in olanzapine group, and 32% in clozapine group, respectively. Significant differences were noted in areas of desire, arousal, erection, and ejaculation in risperidone group as compared olanzapine and clozapine groups.

Prolactin levels were also found to be significantly high in risperidone group in comparison to olanzapine and clozapine groups. This also positively correlated in Pearson’s correlation test, with all the subscales of SFQ viz., dysfunctional desire ($r = 0.29, P = 0.006$), arousal ($r = 0.36, P < 0.001$), erection ($r = 0.4, P < 0.001$), ejaculation ($r = 0.39, P < 0.001$), as well as neurological ($r = 0.28, P = 0.02$), and other ($r = 0.23, P = 0.01$) side effects of UKU scale.

Table 1: Sample characteristics for sociodemographic variables (n=103)

| Variable          | Olanzapine (n=31) (%) | Risperidone (n=23) (%) | Clozapine (n=19) (%) | Control (n=30) (%) |
|-------------------|-----------------------|------------------------|----------------------|--------------------|
| Religion          |                       |                        |                      |                    |
| Hindu             | 29 (93.6)             | 20 (86.9)              | 17 (89.4)            | 29 (96.6)          |
| NonHindu          | 2 (6.4)               | 3 (13.0)               | 2 (10.6)             | 1 (3.3)            |
| Ethnicity         |                       |                        |                      |                    |
| Tribal            | 10 (32.25)            | 4 (17.39)              | 5 (15.78)            | 1 (3.3)            |
| Nontribal         | 21 (67.74)            | 19 (82.6)              | 16 (84.21)           | 29 (96.6)          |
| Occupation        |                       |                        |                      |                    |
| Farmer            | 22 (70.96)            | 16 (69.56)             | 13 (68.42)           | 12 (40)            |
| Others            | 9 (29.0)              | 7 (30.43)              | 6 (31.57)            | 18 (60)            |
| SES               |                       |                        |                      |                    |
| Lower             | 26 (83.87)            | 18 (78.26)             | 16 (84.21)           | 19 (63.3)          |
| Middle            | 5 (16.12)             | 5 (21.73)              | 3 (15.78)            | 11 (36.6)          |
| Family type       |                       |                        |                      |                    |
| Nuclear           | 11 (35.48)            | 4 (17.39)              | 5 (26.31)            | 10 (33.3)          |
| Extended          | 20 (64.51)            | 19 (82.60)             | 14 (73.68)           | 20 (66.6)          |
| Domicile          |                       |                        |                      |                    |
| Rural             | 24 (77.41)            | 17 (73.91)             | 15 (78.94)           | 18 (60)            |
| Urban             | 7 (22.58)             | 6 (26.08)              | 4 (21.05)            | 12 (40)            |
| Diagnosis         |                       |                        |                      |                    |
| Paranoid          | 21 (67.74)            | 15 (65.21)             | 12 (63.15)           |                    |
| Undifferentiated  | 5 (16.12)             | 4 (17.39)              | 6 (31.57)            |                    |
| Unspecified       | 5 (16.12)             | 4 (17.39)              | 1 (5.26)             |                    |
| THP               |                       |                        |                      |                    |
| Yes               | 11 (35.48)            | 20 (86.95)             | 7 (36.84)            |                    |
| No                | 20 (64.51)            | 3 (13.04)              | 12 (63.15)           |                    |

THP – Trihexyphenidyl; SES – Socioeconomic status
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Table 2: Sample characteristics for sociodemographic and clinical variables

| Variables                  | Mean±SD       | Olanzpine (n=31) | Risperidone (n=23) | Clozapine (n=19) | Control (n=30) | F     | P    |
|----------------------------|---------------|------------------|-------------------|------------------|----------------|-------|------|
| Age (years)                | 32.97±7.74    | 34.52±8.66       | 36.05±6.77        | 37.8±36.3        | 1.44            | 0.236 |
| Education (years)          | 9.45±4.77     | 11.56±3.27       | 10.9±3.8          | 9.87±4.73        | 1.29            | 0.282 |
| Illness duration (in years)| 5.26±4.38     | 4.86±3.75        | 6.18±4.12         | 0.55±1.02        | 0.571           | 0.579 |
| CPZ equivalent (in mg/day) | 269.35±146.44 | 207.61±101.53    | 248.68±120.32     | 1.572±0.21       | 1.572           | 0.215 |
| Treatment duration (in months)| 0.09±9.24 | 0.25±0.19        | 0.15±8.79         | 0.72±0.05        | 0.770            | 0.467 |
| BPRS                       | 19.1±0.84     | 19.52±0.89       | 19.05±7.39        | 2.179±0.12       | 2.179           | 0.121 |
| Pulse (per min)            | 76.00±5.46    | 75.65±4.49       | 73.78±5.20        | 0.724±0.54       | 0.724           | 0.540 |
| Systolic BP (in mmHg)      | 119.1±4.64    | 119.65±4.99      | 119.47±3.99       | 1.016±0.92       | 1.016           | 0.922 |
| Diastolic BP (in mmHg)     | 79.09±4.67    | 80.17±3.66       | 80.00±3.83        | 0.364±0.77       | 0.364           | 0.779 |
| Weight (in kg)             | 60.64±2.64    | 59.71±4.90       | 59.15±3.27        | 0.671±0.57       | 0.671           | 0.572 |
| Height (in cm)             | 162.94±3.37   | 160.91±4.47      | 160.95±3.027      | 1.732±0.16       | 1.732           | 0.165 |
| BMI                        | 22.87±1.3     | 23.09±2.1        | 22.87±1.7         | 0.118±0.94       | 0.118           | 0.949 |

BPRS – Brief Psychiatric Rating Scale; BMI – Body mass index; SD – Standard deviation; CPZ – Chlorpromazine; THP – Trihexyphenidyl; BP – Blood pressure

Table 3: Frequency of drug side effects (including sexual dysfunction and hyperprolactinemia) across the three study groups

| Variables                | Olanzpine (n=31) (%) | Risperidone (n=23) (%) | Clozapine (n=19) (%) | χ²   | P    |
|--------------------------|----------------------|------------------------|----------------------|-------|------|
| UKU psychic              | 18 (58.1)            | 10 (43.5)              | 14 (73.7)            | 3.89  | 0.14 |
| UKU neurological         | 5 (16.1)             | 12 (52.2)              | 0 (0)                | 17.4  | <0.001** |
| UKU autonomic            | 0 (0)                | 0 (0)                  | 18 (94.7)            | 67.9  | <0.001** |
| UKU others               | 31 (100)             | 23 (100)               | 19 (100)             | 0     | 1    |
| SFQ desire               | 19 (61)              | 18 (78)                | 7 (37)               | 7.478 | 0.024* |
| SFQ arousal              | 19 (61)              | 20 (87)                | 7 (37)               | 11.281 | 0.004** |
| SFQ ejaculation/erection | 14 (48)              | 19 (83)                | 6 (32)               | 12.367 | 0.002** |
| SFQ orgasm               | 3 (9.67)             | 0 (0)                  | 0 (0)                | 4.239 | 0.07# |
| SFQ ejaculation/erection | 16 (52)              | 19 (83)                | 6 (32)               | 11.458 | 0.003** |
| SFQ total                | 18 (58.3)            | 20 (87)                | 6 (32)               | 13.436 | 0.001** |
| Prolactin                | 14 (45.2)            | 20 (87)                | 10 (52.6)            | 34.662 | <0.001** |

*Significant at level 0.05; **Significant at level 0.01; # Cell count <5. Fisher’s exact test applied SFQ. SFQ – Sexual functioning questionnaire; UKU – Udvalg for Kliniske Undersøgelser

No significant difference was noted in any other blood parameters such as KBS, urea, creatinine, T₃, T₄, and TSH among the different study groups.

DISCUSSION

In this study, 86% reported sexual dysfunction in risperidone group as compared to 48.3% in olanzapine group and 31% in clozapine group, respectively. Thus, it replicated the findings of the previous study with a cross-sectional design in which Nagaraj et al.[6] found that 96% in risperidone group reported sexual dysfunction as compared to 88% in quetiapine and 90% in the olanzapine group, respectively. This finding strengthens the observation done by Wirshing et al.[8] and Fortier et al.[17] that compared risperidone with clozapine and olanzapine.

An Indian study by Nebhinani et al.[8] also noted similar finding that sexual dysfunction was highest for risperidone, followed by trifluoperazine and olanzapine.

Recent Indian study[7] which assessed the prevalence of sexual dysfunction in patients with mental illness receiving psychotropic medication using sexual functioning using Psychotropic-Related Sexual Dysfunction, noted that presence of sexual dysfunction is more common among subjects who are receiving long-term antipsychotic treatment as compared to patients who were on antidepressant. However, the limitation of the study was they did not mention a category of antipsychotics like typical versus atypical or not used any biological parameters and also sample size was smaller.[7]

In our study, 61% in olanzapine, 78% in risperidone, and 37% in clozapine groups reported decreased sexual desire and this supports the findings noted by Hummer et al.,[9] and Wirshing et al.[16] Impaired desire is the most frequently reported sexual dysfunction among all the medication groups in this study that has been previously reported by Aizenberg et al.,[18] Lingjaerde et al.,[22] Smith et al.,[13] and Aizenberg et al.[3] An Indian study also noted reduced libido was the most common sexual side effect in patients who are on risperidone.[8]

An assessment of changes in libido associated with psychotropic medications can be difficult because psychiatric illnesses can significantly affect sexual interest. The effects of antipsychotics on libido are not, as well
characterized as other forms of sexual dysfunction, because of the difficulty in measuring changes in libido. Several other factors like patient’s socioeconomic status and quality of life can influence his libido. However, it would be difficult to conclude that drugs are entirely responsible for the higher rate of impaired libido in the study because we cannot exclude the role of illness sharing to some extent in the impairment of libido experienced by the patients.

In this study 61% and 48% in olanzapine, 87% and 83% in risperidone, and 37% and 32% in clozapine groups reported difficulty in arousal and erectile functions, respectively. Both being highest in the risperidone group.

These findings are in agreement with the report of Kotin et al. and MacDonald et al. that erectile dysfunction (ED) is the most commonly reported sexual dysfunction. However, in the study by Nagaraj et al., patients on olanzapine reported more ED (50%) as compared to risperidone (40%) and quetiapine (36%) but it was not statistically significant. Previous studies comparing sexual dysfunction between atypical and typical antipsychotics have not found any significant difference in erectile functioning. Wirshing et al. paradoxically reported that ED with risperidone was highest as compared to clozapine and haloperidol/fluphenazine group. This could be explained by the hyperprolactinemic effect of risperidone that was found to be higher than haloperidol or clozapine. It is easier for the patient to appreciate and report his erectile problems compared to diminished libido. This could also have led to higher reporting of ED in all these studies.

In this study, 52% in olanzapine, 83% in risperidone, and 32% in clozapine groups reported orgasmic/ejaculatory dysfunction, respectively. This was in comparison with the study by Wirshing et al., in which 86% of the patients on risperidone reported difficulties in ejaculation/orgasm as compared to 20% in clozapine group. However, the sample was too small (n = 14 for risperidone and n = 5 for clozapine). In the study by Kelly and Conley found that patients on quetiapine had better orgasmic quality and ability compared to risperidone and fluphenazine.

In our study, patients on risperidone reported highest level of orgasmic/ejaculatory dysfunction and the duration of treatment were beyond 6 months, in fact, more than a year in many of them and this could explain the difference in impairment of orgasm in comparison to other studies.

Our study is unique in the sense that, it included RBS, blood urea, serum creatinine, and thyroid profile to assess the general physical health of the patients. We never come across any studies that included these parameters in their assessment. However, we have come across many studies that included the effect of antipsychotics on serum prolactin level.

In this study, elevated prolactin level was statistically significant in risperidone group followed by clozapine and olanzapine groups respectively. This is in support of the literature that risperidone was associated with a higher level of prolactin elevation and thus leading to higher level of sexual dysfunction as compared to other atypical antipsychotics. This also supports the findings of the study by Turonne et al., in which risperidone was associated with a higher level of prolactin elevation compared to olanzapine and clozapine. This complies with the hypothesis that risperidone is associated with significantly higher dysfunction in all four stages of the sexual cycle, owing to its hyperprolactinemic properties.

CONCLUSION

On the basis of the available literature and results of the index study, substantiating the earlier findings, it can be concluded that:

1. Sexual dysfunction is more common in patients taking risperidone
2. Risperidone is most frequently associated with neurological side effects compared to other atypical antipsychotics
3. Prolactin elevation and associated sexual dysfunction are more in patients taking risperidone
4. Routine enquiry about sexual symptoms prior to the prescription of antipsychotics and on follow-up would improve overall satisfaction and adherence to treatment.

Limitations and future directions

This study included only male married patients with schizophrenia. Thus, gender specific results could not be generalized for the whole schizophrenic population. In the future studies female patients with schizophrenia should be included so that gender differences in sexual dysfunction can be generated.

Scales used in this study were not earlier standardized in the Indian population in local languages which could also be considered as a limitation of our study. The sexual dysfunction in these patients cannot be directly attributed to the drugs alone as an initial assessment to the start of antipsychotic was not done. Temporal relationship between prolactin, sexual dysfunction, and antipsychotic use was not studied. Thus making it difficult to conclude hyperprolactinemia as the mediator of sexual dysfunction and antipsychotics.

Objective evidence of sexual dysfunction using nocturnal penile tumescence, penile plethysmography, and seminal fluid analysis would further validate the scales in future studies.
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Conflicts of interest

There are no conflicts of interest.

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