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Sexual Dysfunction with Olanzapine in Male and Female Patients of Schizophrenia

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Abstract: ***Background: Since the launch of antipsychotic drugs, sexual side-effects have become one of the most important determinants of treatment compliance. Studies regarding sexual side-effects associated with antipsychotics comprise only a handful in the Indian population, especially so in this north-eastern part of the country. AIMS AND Objectives: 1) To assess the sexual dysfunction associated with olanzapine in male and female patient of Schizophrenia. 2) To compare the sexual dysfunction associated with olanzapine between male and female patients of Schizophrenia. Materials and Methods: This was a hospital based comparative study conducted on 50 clinically stable male and female patients of Schizophrenia on olanzapine only. A Sexual Functioning Questionnaire (SFQ) was administered after assessing the clinical stabilities with the Brief Psychiatric Rating Scale (BPRS). Sexual dysfunction was assessed by calculating the mean scores on all the domains of sexual functioning in SFQ which were then compared across the study groups using the Chi square test. The results were analysed using SPSS Version 16.0 setting the significance threshold at p <0.05. Results: When compared in male and female patients, Olanzapine was seen to cause more sexual desire disorders, more arousal disorders, more orgasmic difficulties and a more overall sexual dysfunction in males. In females, Olanzapine led to more sex-related pain disorders. Olanzapine induced sex-related pain disorders was found to be significant when compared between males and females (p=0.021). Conclusion: Sexual dysfunction can be caused by antipsychotic drugs. So clinicians should try to address these side-effects to help patients' attain a better compliance.***

Keywords: Sexual dysfunction, Olanzapine, Schizophrenia

1. Introduction

An important determinant of one's quality of life is sexual function or sexuality. WHO defines *sexual health* as "integration of physical, emotional, intellectual & social aspects of sexual being in ways that are positively enriching & that enhance personality, communication & love. Every person has a right to receive sexual information & to consider sexual relationship for pleasure as well as for procreation."(WHO Technical Report, Series 572).[1] According to Aizenberg et al 1995,Marques et al 2012, Fujii et al 2010, Malik et al 2011, sexual dysfunction in patients with schizophrenia may be due to the disease process itself (example negative symptoms), physical health or use of psychotropic medications.[2,3,4],

According to ICD 10, the schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and by inappropriate or blunted affect. Clear consciousness and intellectual capacity are usually maintained, although certain cognitive deficits may evolve in the course of time. The normal requirement for a diagnosis of schizophrenia is a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) below, or symptoms from at least two of the groups referred to as (e) to (h), should have been clearly present for most of the time during a period of 1 month or more. [5]

a) Thought echo, thought insertion or withdrawal, and thought broadcasting;
b) Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations;delusional perception;
c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);
e) Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end;
f) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms;
g) Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication;
i) A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

Baggaley et al in 2008 also found that risperidone induces sexual dysfunction most frequently followed by haloperidol, olanzapine, quetiapine & least by aripiprazole. [6] Knegtering et al 2003, 2004, 2006, 2008 & Boer et al 2011- too found a

comparable order – in the following ascending array- risperidone, haloperidol, olanzapine, quetiapine & aripiprazole. [7,8,9,10,11]

Olanzapine is a thienobenzodiazepine. Half life of olanzapine is 31 hours. Olanzapine is an antagonist at serotonin 5HT2a and 5HT1a, dopamine $D_{2,1,4}$, alpha-1 adrenergic, muscarinic $M_{1\text{-}5,}$ and histamine H_1 receptors. [12]

Around half of all patients treated with antipsychotics experience sexual dysfunction; the associated distress and frustration may have a profound effect on the quality of life of the patient as well as making personal relationships more difficult, and sexual dysfunction may lead to non-compliance with the antipsychotic treatment regimen. [13]. Finn et al (1990) showed that patients are more concerned with the sexual side-effects of their medications than any other side-effect.[14] Structured interviews reveal 30 to 60% of sexual side effects associated with antipsychotic treatment (Knegtering 2008 & 2003, Lingjaerde et al 1987, Sullivan & Lukoff et al 1990, Dossenbach et al 2005).[15,16,17]

As already mentioned, when a person is able to experience desire, arousal & orgasm, he is said to have a normal sexual function. Hence an abnormal sexual function or in other words sexual dysfunction is an inability or a diminution of sexual desire, arousal or orgasm. [1] Sexual dysfunctions can be broadly divided into- desire disorders, arousal disorders, orgasmic disorders and pain disorders (Infrasca 2011).[1]

According to the current classification established by the American Psychiatric Association, disorders of sexual function are divided into 4 categories:

1) Disorders of sexual desire,
2) Disorders of arousal,
3) Disorders of orgasm and
4) Sexual pain disorders (American Psychiatric Association 1994).

William Howell Masters and Virgnia Johnson gave the model of sexual response cycle in 1966. According to this model the sexual response cycle consists of four phases- excitement, plateau, orgasm and resolution.[18]

According to Meston & Frohlich 2000, the sexual response cycle can be classified into four phases- sexual desire, sexual arousal, orgasm & resolution or refraction.[19]

Serrati & Chiesa 2011 reported 12 to 38% decrease in desire with antipsychotics. Knegtering et al 2008, Boer et al 2011 found 6 to 50% reduction in sexual desire with the use of antipsychotic medications. Aizenberg et al 1995 reported a diminution in sexual desire in patients using antipsychotics that in those not using antipsychotics.[8,11,20] Patients being treated with antipsychotics often report being less easily sexually aroused (Aizenberg et al 1995).[21] The meta-analysis of Serrati & Chiesa 2011 shows that 7 to 46% of patients using antipsychotics experience dysfunction of arousal like erection & lubrication. Knegtering et al 2008, Boer et al 2011 reported 0 to 39% for the same. [8,11,20] Knegtering et al 2008, Serrati & Chiesa 2011 reported a decrease in vaginal lubrication with the use of antipsychotic drugs.[8,20]

Studies by Serrati and Chiesa in 2011 revealed 4 to 49% of orgasmic dysfunctions with antipsychotics. Another study done by Knegtering et al 2008, Boer et al 2011revealed 3 to 46%(3% for olanzapine) of orgasmic disturbances with antipsychotic use. Ghadirian et al in 1982 also reported a disturbance in quality of orgasm with use of antipsychotic medications.[8,11,20] Pain during orgasm with the use of antipsychotic drugs was reported by Ghadirian et al 1982 whereas Berger et al in 1979 and Donnellan et al in 2001reported painful ejaculation in patients using antipsychotics.[22,23]

Most antipsychotics are potent dopamine blockers leading to sustained elevation of prolactin (Knegtering et al 2008,Ghadirian et al 1982)[8] and this increase in prolactin inhibits tuberoinfundibular dopaminergic neurons leading to sexual disturbances (Fitzgerald and Dinan 2008).[24] Studies have also revealed significant contribution of dopaminergic, adrenergic, serotonergic and cholinergic actions of antipsychotics for sexual dysfunction. [25] In fact a recent study has reported that the mostly responsible mechanism of sexual dysfunction is the direct consequence of dopamine antagonism.[26]

Aims and Objectives

1) To assess the sexual dysfunction associated with olanzapine in male and female patients of Schizophrenia.
2) To compare the sexual dysfunction associated with olanzapine between male and female patients of Schizophrenia.

2. Methods and Materials

This was a hospital based comparative study carried out in a tertiary medical institution located in the upper part of Assam, India. The study duration was one year (August 2016-July 2017). The study received the ethical approval from the institutional review board. An informed written consent was obtained from every participant and they were free to withdraw their consent at any point of time. The total sample size was 50 (30 males and 20 females). The cases were selected from patients, attending the outpatient department or admitted in the institution between August 2016 and July 2017, who were diagnosed as **Schizophrenia** and were on **olanzapine** tablets only, as per ICD-10, who fulfilled the inclusion and exclusion criteria and gave an informed written consent for participating in the study. The diagnosis was confirmed by consultant Psychiatrist of the same institution.

Inclusion Criteria:

- Patients of age group between 18 to 56 years.
- Patients of both the genders.
- Patients who give consent for the study.

Exclusion Criteria:

- Patients with other comorbid medical illnesses like diabetes mellitus, hypertension, cardiovascular diseases, endocrine disorders.

- Patients with comorbid psychiatric illness.
- Patients using alcohol or any other substances.
- Post-menopausal females
- Patients on more than one antipsychotic drug or other drugs that affect sexual functioning like antidepressants are not included. (But trihexiphenidyl was allowed in the patients).

Assessment Tools –

- Informed consent form
- The ICD-10 classification of Mental and Behavioural disorders
- Kuppuswamy's Socio-economic Status Scale (Modified version 2014)
- Semi-Structured Proforma
- Brief Psychiatric Rating Scale (BPRS)
- Sexual Functioning Questionnaire (SFQ)
- Statistical Program for Social Sciences (SPSS) windows version 16.0

Procedure

All patients in the age group of 18 -56 years who attended the outpatient department or who were admitted in the Department of Psychiatry, AMCH within the time period of August 2016 to July 2017, and diagnosed as Schizophrenia as per ICD-10, confirmed by the consultants, maintaining well on tablets **Olanzapine only** for at least 6 weeks were taken. Every consecutive case who attended or who was admitted in the study period was selected till the total sample size was reached. A written informed consent was taken from each participant. They were free to withdraw their consent at any given point of time. A socio-demographic data of each patient was tabulated in the demographic sheet by interview method. After this, clinical stabilities of the patients were assessed with the Brief Psychiatric Rating Scale (BPRS) following which a Sexual Functioning Questionnaire (SFQ) was provided to every patient.

Analysis of the observed data was done using tests like **Chi square test and unpaired t-test** in SPSS windows version 16.0. The significance threshold for the tests were set at **p<0.05**. Pie charts and bar diagram were used for graphical representation of the results.

3. Results and Observations

Table 1: Distribution of Cases on Olanzapine on the basis of age

Age in Years	Cases on Olanzapine	
	N	%
18-30	26	52
31-43	14	28
44-56	10	20

It is seen from the above table that cases were mainly in the age group of 18 to 30 years.

Table 2: Mean age distribution of cases on Olanzapine

	Cases on Olanzapine	
	Mean±SD	Range
Age in Years	33.60±9.602	20-55

Table 3: Distribution of cases on olanzapine according to sex

Sex	Cases on Olanzapine	
	N	%
Male	30	60
Female	20	40

Table 4: Comparison of sexual desire in cases on olanzapine between males and females

SFQ Score for Desire Disorders		Normal (N)(%)	Elevated (N)(%)	p-value
Olanzapine	Male	27 (90%)	3 (10%)	1.000
	Female	18 (90%)	2 (10%)	

*SFQ- Sexual functioning questionnaire
*p-value significant at <0.05

It was seen that with olanzapine, 2 out of 20 females and 3 out of 30 males are affected. On applying chi-square test the p value is found to be 1.000 which denotes that there is no significant statistical difference in sexual desire among males and females.

Table 5: Comparison of sexual arousal in cases on olanzapine between males and females

SFQ Score for Arousal Disorders		Normal (N) (%)	Elevated (N) (%)	p-value
Olanzapine	Male	27 (90%)	3 (10%)	0.265
	Female	20 (100%)	0 (0%)	

*SFQ- Sexual functioning questionnaire
*p-value significant at <0.05

From the above table it is seen that with olanzapine, 0 out of 20 females and 3 out of 30 males are affected. On applying chi-square test the p value is found to be 0.265 which denotes that there is no significant statistical difference in sexual arousal among males and females.

Table 6: Comparison of orgasmic difficulties in cases on olanzapine between males and females

SFQ Score for Orgasmic Disorders		Normal (N) (%)	Elevated (N) (%)	p-value
Olanzapine	Male	21 (70%)	9 (30%)	0.738
	Female	16 (80%)	4 (20%)	

*SFQ- Sexual functioning questionnaire
*p-value significant at <0.05

We can see that 4 out of 20 females and 8 out of 30 males are affected. On applying chi-square test the p value is found to be 0.738 for olanzapine which denotes that there is no significant statistical difference in orgasmic difficulties among males and females.

Table 7: Comparison of sex related pain disorders in cases on olanzapine between males and females

SFQ Score for Pain Disorders		Normal (N) (%)	Elevated (N) (%)	p-value
Olanzapine	Male	30 (100%)	0 (0%)	0.021
	Female	16 (80%)	4 (20%)	

*SFQ- Sexual functioning questionnaire
*p-value significant at <0.05

We can see that 4 out of 20 females and 0 out of 30 males are affected. On applying chi-square test the p value is found to be **0.021** which denotes that there is a significant

statistical difference in sex related pain disorders among males and females.

Table 8: Comparison of overall sexual dysfunction in cases on olanzapine between males and females

SFQ Score for Overall Sexual Dysfunction		Normal (N) (%)	Elevated (N) (%)	p-value
Olanzapine	Male	24 (80%)	6 (20%)	0.219
	Female	19 (95%)	1 (5%)	

*SFQ- Sexual functioning questionnaire
*p-value significant at <0.05

We can see that 1 out of 20 females and 6 out of 30 males are affected. On applying chi-square test the p value is found to be 0.219 which denotes that there is no significant statistical difference in overall sexual disorders among males and females between the groups.

4. Discussion

Most of the subjects in the group belonged to the age group 18-30 years. The mean age was **33.60±9.602** years. There was no significant difference between the mean ages. Majority of subjects were males (**60%**). There was no significant difference when it comes to distribution of subjects in both the groups on the basis of gender.

Our results corroborate with the meta-analysis of Serretti and Chiesa which shows that with olanzapine, the count is 14-77% for desire disorders [20], 9-50% for arousal disorders, 3-61% for orgasmic disorders and 13-61% for sexual dysfunction.[20]

So we can infer that in females, olanzapine leads to more orgasmic difficulties and more sex related pain disorders in females. In case of males, olanzapine leads to more desire disorders. Although none of the other findings were statistically significant, yet with olanzapine, sex-related pain disorders was found to be significant when compared between males and females **(p= 0.021).** The present findings corroborate with the findings of Ghadirian who concluded that pain during orgasm occurred with the use of antipsychotic drugs,[22] although he did not mention the group of antipsychotic tested.

5. Conclusion

With the advent of psychopharmacology, a question was perpetually posed as regards the outweighing side effects of psychotropic medications, mostly antipsychotics. Most importantly sexual side effects came to be viewed as a means of non-compliance and hence, relapse. Thus this study tried to find out if sexual side effects were caused by antipsychotic medications and if so, to what extent. Olanzapine led to more orgasmic difficulties and more sex related pain disorders in females. In case of **males,** olanzapine led to more desire disorders. Olanzapine induced sex-related pain disorders was found to be significant when compared between males and females **(p=0.021).** However future research in this area is mandatory to validate our finding in this regard. Limitations in this study includes that here an initial assessment of participants' sexual dysfunction before treatment was not assessed. Thus, it is difficult to distinguish psychotropic-induced sexual dysfunction if they were already having any sexual problems pre-morbidly. Also self-reporting scales were employed in the study and although scales were reported to be well correlated with observer's ratings, there is a possibility of discrepancies between self-reports and actual problems. Besides self-reports have been subjected to biases.

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