

A Comparative Study of Sexual Dysfunction due to Typical and Atypical Antipsychotics in Remitted Bipolar-I Disorder

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ABSTRACT

In the remitted phase of bipolar I disorder, sexual dysfunction is commonly due to drugs used in the treatment rather than the disease itself. There are very few studies, especially in the Indian population, addressing the frequency of sexual dysfunction due to antipsychotics in bipolar I disorder. Hence this study was done to determine the sexual dysfunction due to antipsychotics and to compare the same among typical and atypical antipsychotics. A cross sectional study with 108 male patients of remitted bipolar I disorder (DSM-IV), chosen by purposive sampling technique was done. Psychopathology was assessed using the Brief Psychiatric Rating Scale, Structured Interview Guide for the Hamilton Depression Rating Scale and Young Mania Rating Scale. Sexual side effects due to antipsychotics were assessed using the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale. The total sample size was divided into two groups of those on typical antipsychotics (n = 53) and atypical antipsychotics (n = 55). The two groups were compared for sexual dysfunction using Chi-square test. Results showed dysfunction in at least one phase of the sexual response cycle, comprising of desire, arousal and orgasm, was present in 66% of the sample population. Erectile dysfunction was present in 42% of the sample population and it was the most common type of sexual dysfunction reported. It was also significantly different across the two groups (p = 0.025). There was no significant difference in other aspects of sexual dysfunction across the two groups. In conclusion patients of Bipolar I disorder experience sexual side effects of antipsychotics frequently. Erectile dysfunction is the most common sexual dysfunction among men and this is significantly higher with typical than atypical antipsychotics.

Introduction

Sexual function is our physiologic capacity for desire, arousal and orgasm. In women, low sexual desire is the most common problem and for men, it is erectile dysfunction (Bancroft, 1989). Sexual dysfunction can result from a wide variety of psychological and physical causes and a variety of drugs including antipsychotics.

Antipsychotics being the mainstay in the treatment of schizophrenia, sexual dysfunction due to antipsychotics has been currently studied extensively in this patient group (Burke et al., 1994; Aizenberg et al., 1995; Smith et al., 2002; MacDonald et al., 2003). The primary underlying mechanism is likely to be the direct dopamine antagonist effect (Gitlin, 1994). Serotonin mechanisms are also important in antipsychotic treatment and its relationship to sexual dysfunction. (Meston & Frohlich, 2000). Further, Hummer et al. (1999), Wirshing et al. (2002), Bobes et al. (2003) and Aizenburg et al. (2001) have compared the sexual dysfunction due to typical and atypical antipsychotics in the patients of schizophrenia. Except for the latter, the other studies have not found overall sexual dysfunction to

be significantly different across the two groups.

Even in bipolar I disorder, the major impact on impaired sexual functioning is due to antipsychotics and antidepressants. There are abundant studies of sexual dysfunction due to antidepressants, but the long term use of antipsychotics in bipolar I disorder itself being less studied (Taylor et al., 2003), research on sexual dysfunction due to antipsychotics in this patient population is meager, especially so in the Indian population. Some studies selecting mixed patient population (affective and non-affective psychosis) have revealed that in affective psychosis, sexual dysfunction is less than that of non-affective psychosis (Lingjaerde et al., 1987; Kockott & Pfeiffer, 1996; Raja & Azzoni, 2003). So this study was aimed at studying the frequency of sexual dysfunction due to typical and atypical antipsychotics and to compare the two in remitted bipolar I disorder.

METHOD

Study design and sample

The index study was conducted at the Central Institute of

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Psychiatry, Ranchi. It was a cross-sectional hospital based study. The subjects were recruited for the study by the purposive sampling technique. The study sample consisted of 108 male patients of remitted bipolar I disorder, meeting the DSM-IV criteria, aged between 18-50 years, having sexual activity for the past one month, on regular treatment with an antipsychotic (typical or atypical) for at least six weeks and giving informed consent. They were divided into two groups- group I consisted of 53 patients on typical antipsychotics and group II of 55 patients, on atypical antipsychotics. Patients with co-morbid medical disorder (diabetes mellitus, hypertension etc and on treatment for the same) or organic diseases (urological conditions, lymphatic diseases of the penis etc) known to cause sexual dysfunction, having primary sexual dysfunction, having concurrent psychiatric diagnosis known to affect sexual functioning (alcohol and other substance dependence, schizoaffective disorder etc) and symptomatic patients were excluded from the study.

Assessments

After collecting the required socio-demographic and clinical data from the patients, they were rated on Young Mania Rating Scale (YMRS) (Young et al., 1978), Structured Interview Guide for the Hamilton Depression rating scale (SIGH-D) (Janet and Williams, 1988) and Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1988) to determine the remission status. Patients with SIGH - D score more than seven and/or YMRS score more than four and having active psychopathology as assessed by BPRS were not included in the study.

Subsequently they were rated on the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale (Lingjaerde et al., 1987) to determine the sexual dysfunction in all spheres including desire, erection, ejaculation and orgasm.

In the UKU Scale, there are ten items that rate the presence and severity of reproductive and sexual side effects, namely menorrhagia, amenorrhoea, galactorrhoea, gynaecomastia, increased sexual desire, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction and dry vagina. Each item is rated on a scale of 0 to 3. For the purpose of statistical analysis, patients with a score of one or higher on the items related to sexual functioning of the UKU side effect rating scale were considered. Further total scores on the four subgroups of psychic, autonomic, neurological and other side effects were analysed to determine the spectrum of side effects due to antipsychotics.

Analysis

Descriptive statistics was applied to describe the frequency of sample distribution. Mann-Whitney U test was applied to see the group differences in socio-demographic and clinical variables and the Chi-square test was applied to see whether the use of concurrent medicines differed across the two groups and to compare the sexual dysfunction across the two groups.

RESULTS

Socio-demographic and clinical characteristics

With respect to the various socio-demographic variables like religion, occupation, marriage etc, the two groups were not differing significantly. Further none of the clinical variables like age, duration of illness, number of episodes, period of remission and duration of treatment were found to be differing significantly across the two groups. But the autonomic side effects were found to be significantly higher among those on typical antipsychotics. The total scores on the various tools used in the study also did not differ significantly across the two groups. The clinical variables are represented in tables 1 and 2.

Medication used by the study groups

In group I, 26 patients were on chlorpromazine, 23 were on haloperidol, 2 patients were on trifluoperazine and 1 patient was on thioridazine. One patient on trifluoperazine was also on depot fluphenazine. In group II, 48 patients were on olanzapine, 5 patients were on risperidone and two were on clozapine. The mean chlorpromazine equivalent of typical and atypical antipsychotics were calculated to be 319.29 ± 231.22 mg and 277.04 ± 213.47 mg respectively. However the chlorpromazine equivalent dose was not found to be significantly differing across the two antipsychotic groups ($p=0.326$).

A total of 50 patients were concurrently on trihexyphenidyl out of which 38 patients were on typical antipsychotics. This was expected as trihexyphenidyl is often needed to control the troublesome extrapyramidal side effects associated with the typical antipsychotics. Lithium was the mood stabilizer used commonly by the patients ($n=60$). Sodium valproate ($n=21$), carbamazepine ($n=23$) and lamotrigine ($n=1$) were the other mood stabilizers used. Three patients were not on any mood stabilizers and out of the remaining 105 patients, 16 were on a combination of two mood stabilizers. Both the groups were evenly

Table 1:

GROUP DIFFERENCE OF CLINICAL VARIABLES

Variables	Mean rank of antipsychotic groups		Sum of ranks of antipsychotic groups		z	p
	n1 (53)	n2 (55)	n1 (53)	n2 (55)		
Age (yrs)	57.10	51.99	3026.50	2859.50	1.070	0.396
Duration of illness (months)	53.12	55.83	2815.00	3070.50	0.880	0.653
No of episodes	54.08	54.90	2866.50	3019.50	0.868	0.890
Duration of last episode (months)	54.74	54.27	2901.00	2985.00	0.880	0.938
Remission (months)	50.85	58.02	2695.00	3191.00	0.195	0.233
Duration of treatment (months)	52.58	56.35	2786.50	3099.50	0.532	0.530
Mann Whitney - U test						
p = NS						
n1 = Typical antipsychotic group						
n2 = Atypical antipsychotic group						

Table 2:

GROUP DIFFERENCE OF TOTAL SCORES ON THE VARIOUS RATING SCALES

Variables	Mean rank of antipsychotic groups		Sum of ranks of antipsychotic groups		z	p
	n1 (53)	n2 (55)	n1 (53)	n2 (55)		
YMRS total score	54.48	54.52	2887.50	2998.50	0.007	0.994
SIGH-D total score	57.43	51.67	3044.00	2842.00	0.970	0.332
BPRS total score	55.75	53.30	2954.50	2931.50	0.413	0.679
UKU – total psychic side effects	58.22	50.92	3085.50	2800.50	1.227	0.220
UKU – total neurologic side effects	58.25	50.89	3087.00	2799.00	1.360	0.174
UKU – total autonomic side effects	60.18	49.03	3189.50	2696.50	2.040	0.041 *
UKU – total other side effects	54.87	54.15	2908.00	2978.00	0.122	0.903
UKU – total side effects score	58.51	50.64	3101.00	2785.00	1.310	0.190
Mann Whitney - U test						
p * = 0.05 level of significance						
** = 0.01 level of significance						
n1 = Typical antipsychotic group						
n2 = Atypical antipsychotic group						

matched as far as the usage of all the mood stabilizers was concerned. Chi-square test did not reveal any significant difference in the usage of different mood stabilizer across the two groups. This is represented in table 3.

Comparison of sexual dysfunction

The total scores in the section of sexual side effects of UKU side effect rating scale are compared in the table 4. Erectile dysfunction was the most commonly reported sexual

dysfunction and was seen in 41.7% of the total population. This was significantly high among those on typical antipsychotics (p = 0.025).

39 percent of the total population reported reduced libido, 17.6% reported ejaculatory dysfunction and 14.8% were found to have orgasmic difficulties. Overall, 66% of the patient population were having at least one type of sexual dysfunction. Apart from erectile dysfunction, there was no significant difference across the two groups in the other aspects of sexual dysfunction as shown in the table 5.

Table 3:

**MOOD STABILIZERS AND TRIHEXYPHENIDYL ACROSS TYPICAL
(n=53) AND ATYPICAL ANTIPSYCHOTICS (n=55)**

Sl. No.	Drug	Typical n (53)	Atypical n (55)	Total N (108)	χ^2	df	Exact sig. (2-sided)
1.	Patients receiving one or more mood stabilizers	52	53	105	2.146	2	0.342
2.	Trihexyphenidyl	38	12	50	27.009	1	0.000**

*=0.05 level of significance
**=0.01 level of significance

DISCUSSION**Methodological considerations**

The present study is a single contact hospital based study done to test the hypothesis formulated based on available literature and aimed at assessing the sexual dysfunction due to antipsychotics in bipolar I disorder and comparing the sexual dysfunction due to typical and atypical

Table 4:

**TOTAL SCORES IN THE SECTION OF SEXUAL
SIDE EFFECTS OF UKU SIDE EFFECT
RATING SCALE ACROSS THE TWO GROUPS**

Scores on UKU	Typical n (%)	Atypical n (%)
.00	16 (30.2)	21 (38.2)
1.00	7 (13.2)	9 (16.4)
2.00	9 (17.0)	10 (18.2)
3.00	8 (15.1)	5 (9.1)
4.00	9 (17.0)	8 (14.5)
5.00	3 (5.7)	2 (3.6)
6.00	1 (1.9)	-
Total	53 (100.0)	55 (100.0)

antipsychotics. The subjects attending the outpatient department of C.I.P. were recruited by purposive sampling technique. The cross sectional study design has an advantage over the prospective studies that the problem of attrition is nil. When compared to retrospective studies, the data is more reliable in cross sectional studies. Similar study design has been preferred in many other studies like Kotin et al. (1976), Lingjaerde et al. (1987), Aizenberg et al. (1995), Smith et al. (2002), Aizenberg et al. (2001), Bobes et al. (2003) and MacDonald et al. (2003).

In the present study, all remitted patients were incorporated, as the patients account is less reliable during symptomatic phase. Moreover, the disease itself may contribute to sexual dysfunction in symptomatic phase. The UKU side effect rating scale that has been used to assess the sexual dysfunction was designed by Lingjaerde et al. (1987) and used in a multicentre study with a sample size of 2391, to assess the sexual dysfunction due to antipsychotics. This scale alone has been used in some of the recent studies assessing the sexual dysfunction, like Hummer et al. (1999) and Bobes et al. (2003).

Table 5:

COMPARISON OF SEXUAL DYSFUNCTION ACROSS THE TWO GROUPS

Type of sexual dysfunction	Frequency of sexual dysfunction		Chi-square value	df	Asymp. sig (2-sided)
	Typical (53) n (%)	Atypical (55) n (%)			
Increased Sexual Desire	0 (0)	1 (1.8)	0.973	1	0.324
Diminished Sexual Desire	19 (35.8)	23 (41.8)	0.440	3	0.932
Erectile Dysfunction	28 (52.8)	17 (30.9)	9.379	3	0.025*
Ejaculatory Dysfunction	9 (16.9)	10 (18.2)	0.065	2	0.968
Orgasmic Dysfunction	8 (15.1)	8 (14.5)	1.340	3	0.720

* = 0.05 level of significance

** = 0.01 level of significance

Sample characteristics

The sample size in the present study was 108. Though some studies like Lingjaerde et al. (1987) have assessed huge sample population, majority of studies in this area have similar sample size, ranging from $n = 87$ (Kotin et al., 1976) to $n = 188$ (Kockott & Pfeiffer, 1996).

Since the majority of the sample population were young (mean age : 30 yrs), the confounding bias of increasing age causing more sexual dysfunction is negligible. Larger proportion of married study population is beneficial with respect to more reliable assessment of sexual functioning. This finding is supporting Aizenberg et al. (1995). Average duration of antipsychotic treatment in this study population was seven months. The duration of antipsychotic exposure is an important factor in impaired sexual functioning. This was not significantly differing across the two groups.

Discussion of frequency of sexual dysfunction due to antipsychotics

Erection

In the present study, 45 out of 108 patients (41.7%) had erectile problems, and it is the most common type of sexual dysfunction in this study. Similar results have been reported by the earlier studies like Burke et al., 1994 and MacDonald et al., 2003. Thus erectile dysfunction is found to be the most common sexual dysfunction in men. However the difference in the frequency of erectile dysfunction reported in various studies can be attributed to the differences in the tools used, race, study design and the psychiatric disorder of the patient population.

Other domains of sexual dysfunction

In this study, 71 out of 108 patients complained of sexual dysfunction, that amounts to a frequency of 65.7%, supporting the other studies like MacDonald et al. (2003) & Wirshing et al. (2002). Further, 42 out of 108 patients i.e. 39% reported reduced desire and only one patient who was in full remission, on 10mg of olanzapine and 100mg of lamotrigine reported increased desire. An assessment of changes in libido associated with psychotropic medications can be difficult because psychiatric illnesses can significantly affect sexual interest. The effect of antipsychotics on libido is not as well characterized as other forms of sexual dysfunction, in part because of the difficulty in measuring changes in libido. However, the result of the present study is supporting the Lingjaerde et al. (1987) which has also

reported an impaired libido of 37%. Ejaculatory dysfunction in the present study was about 18% and 15% of the study population reported orgasmic dysfunction, which is similar to that reported by Lingjaerde et al. (1987), Hummer et al. (1999) and MacDonald et al. (2003).

Comparing sexual dysfunction due to typical and atypical antipsychotics

There was a significant difference in erectile problems between the typical and atypical antipsychotic groups, though there was no statistical significance in desire, ejaculation/orgasm and overall sexual dysfunction scores. Atypical antipsychotics were found to be relatively safer with respect to erectile dysfunction. So this study infers that frequency of antipsychotic induced sexual side effects are very high in bipolar I disorder. Significant difference in the area of erectile dysfunction between typical and atypical antipsychotics in the present study is supporting Aizenberg et al. (2001) and Wirshing et al. (2002), carried out in the schizophrenic patient population. Further, in Hammer et al. (1999), Bobes et al. (2003), MacDonald et al. (2003) and Wirshing et al. (2002) all of which were again on schizophrenic population, the overall sexual dysfunction has been found to be not significantly different across the typical and atypical antipsychotics.

Serotonergic mechanisms are found to be as important as dopaminergic mechanisms in sexual functioning. While typical antipsychotics block D_2 receptors and thereby stimulate increased prolactin secretion causing sexual dysfunction, atypical antipsychotics being serotonin-dopamine antagonists, induce their sexual side effects through serotonin mechanisms. This can explain the sexual dysfunction not being significantly different across the two groups in various studies.

Mood stabilizers and sexual dysfunction:

In the present study, 105 out of 108 patients were on mood stabilizers. Lithium was the most commonly used mood stabilizer. Lithium has been studied for sexual dysfunction by Kristensen and Jogensen (1987), Ghadirian et al, (1992) and Aizenberg et al, (1996) in bipolar affective disorder. Studies on lithium concluded that occasionally these patients complain of impaired libido and arousal, but this has not caused distress to them and has not led to treatment non-compliance. Some patients also had spontaneous recovery while on treatment itself. Further, Lingjaerde et al, (1987) inferred that sexual dysfunction is about 10% less frequent among those on lithium along with an antipsychotic as compared to those on antipsychotic alone. However, in the

present study almost all patients were on a combination of antipsychotic and mood stabilizer. Hence such a comparison could not be made. Regarding valproate, there are occasional case reports of reduced libido and arousal in patients of bipolar disorder, but no placebo control studies. Further carbamazepine has been found to reduce the free serum testosterone level in the patients of epilepsy and thereby contributing to impaired libido in some cases. But it also has the property of microsomal enzyme induction, thereby reducing the effective plasma concentration of the drugs used concurrently (eg. haloperidol) and reducing their efficacy. This may indirectly ameliorate the sexual side effects of those drugs. However, the role of mood stabilizers in sexual functioning remain inconclusive.

Clinical implications

1. Sexual dysfunction is frequent among the patients of bipolar I disorder who are receiving antipsychotics.
2. Erectile dysfunction is the most common type of sexual dysfunction among men and this is higher with typical antipsychotics than atypical antipsychotics.
3. Routine enquiry during clinical follow-up interviews regarding sexual dysfunction is essential with respect to drug compliance and disease prognosis.

Limitations

1. Gender specific results could not be generalized in this study as it included only male patients in the sample population.
2. Including a third group of unmedicated patients or those on only mood stabilizer into the study could have provided more reliable results.
3. Some of the individual antipsychotic drugs are not represented adequately because of the relatively small sample size.
4. We did not incorporate the procedures like penile plethysmography and biological markers like serum prolactin level.

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