

## Sexual dysfunction associated with Sertraline and Mirtazapine : A comparative open label study.

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### Abstract

**Introduction:** Antidepressants have become one of the most frequently prescribed drugs in the world. One of the most common side effects impairing the long term compliance for antidepressants is sexual dysfunction. Antidepressants like Sertraline have been associated with higher incidence of sexual dysfunction than Mirtazapine. However, there are studies which show that incidence of sexual dysfunction after use of Mirtazapine may be higher than previously expected. The aim of the study was to assess and compare the incidence of sexual dysfunction after therapy with Sertraline and Mirtazapine in a Nepali population.

**Material And Method:** Patients needing antidepressant therapy but with minimal or no sexual dysfunction at baseline were randomly assigned to either Mirtazapine (n=54, 7.5-30 mg) or Sertraline (n=54, 25-100 mg). Various aspects of sexual functioning at baseline were measured with Change in Sexual Functioning Questionnaire (CSFQ) and the same were reassessed at 4 weeks.

**Results** The incidence of sexual dysfunction seen in 42.9% patients in Sertraline group and 23.7% patients in Mirtazapine group. Sertraline showed significantly greater decline in Orgasm scores than Mirtazapine.

**Conclusion:** Psychiatric referral rate and psychiatry morbidity was low. Sertraline caused significant decline in Orgasm aspect of sexual functioning. Although lesser in propensity, Mirtazapine is not free of adverse effect of sexual dysfunction. More studies are need to further confirm these findings.

**Keywords:** Sertraline, Mirtazapine, Sexual Dysfunction, CSFQ

### INTRODUCTION

Antidepressants have come to become one of the most frequently prescribed drugs in the world. In the United States, the use of antidepressants quadrupled in 20 years and have become the third most commonly prescribed medication as of 2008.<sup>1</sup> Antidepressants are associated with adverse effects like nausea, headache, diarrhea, fatigue, daytime fatigue like insomnia, weight gain and sexual dysfunction. Among them, sexual dysfunction is one of the most common

side effect impairing the long term compliance.<sup>2</sup> In sexual dysfunction, there may be disturbance in any of the four phases of Sexual response cycle (viz. Desire, Excitement, Orgasm and Resolution) including problems in the subjective sense of pleasure or performance.<sup>3</sup> The sexual response is coordinated chemically by the monoamines (dopamine, norepinephrine, and serotonin), neuropeptides (opioid peptides), neurohormones (oxytocin and vasopressin) and neurotrophins.<sup>4</sup> Dopamine is implicated in

sexual interest and desire (libido), nitric oxide and acetylcholine in arousal, serotonin in arousal and orgasm and norepinephrine in orgasm and resolution.<sup>2</sup> SSRIs may impair sexual desire by drug-induced hyperprolactinemia<sup>5</sup> and arousal and orgasm phase of sexual behavior by activation of serotonin 2A (5-HT<sub>2A</sub>).<sup>6</sup>

In a review by Worsham J et al. in 2007, up to 50- 70% of these patients shown to have SSRIs associated sexual dysfunction.<sup>7</sup> In a large study, Only 2% to 7% of patients spontaneously reported sexual side effects, but when a sexual dysfunction questionnaire was used, the incidence of sexual dysfunction rose to 55% for SSRIs.<sup>8</sup> This is expected as patients do not generally open up about their sexual lives commonly. The same study shows that the sexual dysfunction associated with SSRIs significantly higher than atypical antidepressants like Mirtazapine due to mechanism being blockade of 5-HT<sub>2A</sub> receptors.<sup>7</sup> In the study by Montejo et al. 63% of patients receiving Sertraline and only 24.4% experienced sexual dysfunction.<sup>8</sup>

This study tries to evaluate the sexual dysfunctions associated with one SSRI (Sertraline) and an atypical antidepressant (Mirtazapine). This study utilizes a standard questionnaire in evaluating various aspects of sexual functioning. It aims to show whether or not the similar findings can be found in Nepali Outpatients in a tertiary level setting. It also aims to analyze the various unique findings in the study with evidence.

## MATERIAL AND METHOD

This was a prospective randomized open-label study between sexual dysfunction associated with Sertraline and Mirtazapine done at psychiatry Outpatient Department of Tribhuvan University Teaching Hospital.

Inclusion and exclusion criteria: Patients aged 18-65, Without any or with minimal sexual complaints (Change in Sexual Functioning Questionnaire (CSFQ) scores >47 for males and >41 for females) who have been started on either Sertraline or Mirtazapine from TUTH psychiatry OPD were assessed. Patients unwilling or unable to provide information or with significant co-morbid conditions like Diabetes Mellitus, Hypertension, Vascular Illness, current

alcohol or other substance abuse, taking other medications than Sertraline or Mirtazapine, those whose baseline sexual functioning was significantly impaired were excluded from the study.

### Tools:

1) **Semi-structured proforma:** included demographic profile, presenting complaints, findings of general physical and systematic examination followed by mental state examination. Sexual history was included as a special feature in the proforma.

2) **Changes in Sexual Functioning questionnaire-14(CSFQ-14) for males and females:** The CSFQ has 14 questions each uses 5-point Likert scale. Patients self-evaluate their sexual behaviors under headings including: (a) Desire/Frequency, (b) Desire/Interest, (c) Arousal/Excitement, (d) Orgasm/Completion, (e) Pleasure. Higher scores reflect higher sexual functioning. The Nepali version was translated and translated back for cross checking with the help of professional translators. During Interpretation, three methods were used to indicate sexual dysfunction. 1) Score less than cut off of total CSFQ score  $\leq 47$  for males and  $\leq 41$  for females 2) A mean change score of 0.5 on each individual question 3) Total CSFQ score reduction of 3 points. The 1<sup>st</sup> method was used to chose initial patients (i.e only patients with scores above the cut off are chosen). To assess the change in sexual function, mainly the 2<sup>nd</sup> and the 3<sup>rd</sup> method were used in each dimension of sexual functioning and global sexual functioning respectively. Differences were seen using independent and student T-tests(mean scores) or chi square tests(qualitative). ANOVA and Pearson's correlation were done to assess correlations.

### Procedure:

Selected patient were evaluated in terms of semi-structured proforma and diagnosis was made using the criteria used in ICD- 10 DCR. Separate questionnaire for males and females(CSFQ-M and CSFQ-F) were used as assess sexual functioning. Then they were prescribed with either Sertraline or Mirtazapine systematically (Sertraline for odd and Mirtazapine for even serial number). Their sexual functioning was reassessed at one month

of intake of prescribed antidepressant. Ethical clearance was sought from Institutional Review Board (IRB) of Institute of Medicine,(IOM). Informed consent and education regarding the process were provided. No financial burden was incurred on the patients.

**RESULT**

**Table 1: Demographic Characteristic Of Patients**

Parameters	Mirtazapine n =54(%)	Sertraline n=54(%)
<b>Mean age</b>		
Male	27.63±5.86 years	28.19±5.80
Female	27.17±4.67 years	27.5±4.87
<b>Gender</b>		
Male	42(77.8%)	42(77.8%)
Female	12(22.2%)	12(22.2%)
<b>Marital status</b>		
Married	34 (63%)	32 (59.3%)
Single	19(35.1%)	20(37%)
Separated	1(1.9%)	2(3.7%)
<b>Education</b>		
Literate	0(0%)	2(3.7%)
Primary	1(1.9%)	2(3.7%)
Secondary	17(31.5%)	17(31.5%)
Higher	15(27.8%)	11(20.4%)
University	21(38.9%)	22(40.7%)
<b>Religion</b>		
Buddhist	5(9.3%)	6(11%)
Christian	1(1.9%)	3(5.6%)
Hindu	47(87%)	44(81%)
Others	1(1.9%)	1(1.9%)
<b>Diagnoses</b>		
Adjustment	20(37%)	19(35.2%)
Anxiety NOS*	12(22.2%)	12(22.2%)
GAD*	13(24.1%)	13(24.1%)
OCD*	1(1.9%)	3(5.6%)
Panic Disorder	5(9.3%)	2(3.7%)
Social Phobia	1(1.9%)	3(5.6%)
Others	2(3.7%)	2(3.7%)
<b>Lost to follow</b>	16(29.6%)	19(35.2%)

(\*GAD= Generalised Anxiety Disorder  
 \*OCD= Obsessive Compulsive Disorder  
 \*NOS= Not otherwise specified.)

Table 1. shows the demographic profile and characteristics of patients in each treatment arm. The most common patient in each arm was a Hindu married university-educated male with a diagnosis of Adjustment Disorder.

**Table 2: Comparison between Baseline Scores in Sexual functioning Questionnaire (CSFQ-14) scores of participants.**

Category	Mirtazapine		Sertraline		P value	Cut off
	Male					
	Mean	SD	Mean	SD		
Pleasure	2.94	0.56	2.81	0.62	0.435	≤4
Desire (frequency)	7.34	1.12	7.19	1.33	0.622	≤ 8
Desire (interest)	10.22	1.39	10.33	1.66	0.774	≤ 11
Arousal	11.53	1.14	11.70	1.64	0.636	≤ 13
Orgasm	12.09	1.00	11.93	1.30	0.577	≤ 13
Question 10	4.63	0.40	4.48	0.75	0.085	--
Question 14	4.81	0.55	4.85	0.36	0.073	--
Total CSFQ-14 score	53.56	3.13	53.30	4.20	0.782	≤ 47
Female						
Pleasure	2.83	0.75	3.00	0.93	0.725	≤4
Desire (frequency)	7.17	0.75	7.13	0.83	0.925	≤6
Desire (interest)	7.67	0.82	7.63	1.30	0.946	≤ 9
Arousal	9.67	1.21	10.00	1.31	0.636	≤ 12
Orgasm	10.67	1.37	10.63	0.74	0.943	≤ 11
Question 10	4.17	0.41	4.25	0.71	0.802	--
Question 14	4.33	0.82	4.00	0.76	0.445	--
Total CSFQ-14 score	46.50	3.51	46.63	3.29	0.947	≤ 41

Table 2. Baseline scores were statistically comparable in both groups. Most subgroup scores fall under range of sexual dysfunction, except for desire(frequency) scores in females and the total CSFQ scores in both males and females are above the cut-off.

**Table 3. Distribution of patients according to change in scores in Mirtazapine and Sertraline groups.**

Change from baseline	Medication used		Total N=73(100%)	Hypothesized value*	P value
	Mirtazapine n=38(100%)	Sertraline n=35(100%)			
<b>Pleasure</b>				0.5	
0	28(73.7%)	26(74.3%)	54(74.0%)		1
-1 to -2**	3(7.9%)	3(8.6%)	6(8.2%)		
1 to 2	7(18.4%)	6(17.1%)	13(17.8%)		
<b>Desire(Frequency)</b>				1	
0	18(47.4%)	25(71.4%)	43(58.9%)		0.041
-1 to -2	7(18.4%)	1(2.9%)	8(11.0%)		
1 to 2	13(34.2%)	9(25.7%)	22(30.1%)		
<b>Desire(interest)</b>				1.5	
-1	6(15.8%)	5(14.3%)	11(15.1%)		0.653
0	24(63.2%)	18(51.4%)	42(57.5%)		
1	6(15.8%)	9(25.7%)	15(20.5%)		
2	2(5.3%)	3(8.6%)	5(6.8%)		
<b>Arousal</b>				1.5	
0	17(44.7%)	10 (28.6%)	27(37.0%)		0.247
-1 to -2	4(10.5%)	5(14.3%)	9(12.3%)		
1	10(26.3%)	7(20.0%)	17(23.3%)		
2 to 4	7(18.4%)	13(37.1%)	20(27.4%)		
<b>Orgasm</b>				1.5	
0	11(28.9%)	9(25.7%)	20(27.4%)		0.009
-1 to -2	5(13.2%)	4 (11.4%)	9(12.3%)		
1	21(55.3%)	11(31.4%)	32(43.8%)		
2 to 3	1(2.6%)	11(31.4%)	12(16.4%)		
<b>Total CSFQ score</b>				3	
0	9(23.7%)	5(14.3%)	14(19.2%)		0.306
-1 to -2	6(15.8%)	6(17.1%)	12(16.4%)		
1 to 2	14(36.8%)	9(25.7%)	23(31.5%)		
>3	9(23.7%)	15(42.9%)	24(32.9%)		

Total 3(7.9%) patients in each group showed clinically significant change (>0.5) in Pleasure scores. There were no significant difference between the two groups. There was also clinically significant decline in desire (frequency) scores in 13(34.2%) in mirtazapine and 9 (25.7%) in sertraline group. The difference was statistically significant(p=0.041). 13(37.1%) of patients in sertraline group had clinically significant decrease in arousal score (>1.5).

However, the difference between the groups was not statistically significant. In Orgasm score, clinically significant decrease in scores occurred in very few patients (n= 1, 2.6%) in mirtazapine as compared to 11(31.4%) in sertraline group. So, sertraline was seen to affect the orgasm score significantly as compared to mirtazapine. 9(23.7%) patients in Mirtazapine group and 15(42.9%) in Sertraline group had clinically significant decrease in Total CSFQ scores(≥3 points change). However, there was no Statistical significance between the two drugs in this category. Table 3.

There was only weak correlation between drug dose and change in scores. Highest correlation was seen in dose of sertraline and decrease in Desire(Frequency) scores (r=0.557) and the result was statistically significant. (p=0.001). Mirtazapine showed some weak positive correlation with decrease in Desire(Interest) scores with statistical significance(r=0.344, p=0.034). (Table 4)

**DISCUSSION:  
SocioDemography**

The most common demographic profile was that of a male patient of age group 23-27 who was hindu, married, university educated, student with diagnosis of adjustment disorder. This finding is in line with various studies<sup>9,10,11,12</sup> while the finding about educational status is contradicted by the study by UNICEF.<sup>13</sup> The findings and contradictions are explained by the fact that person with aforementioned demographics is more likely to be aware of, concerned about and

open to discuss sexual symptoms with the investigator. Severe mental illness with baseline sexual dysfunction were not included in the study so, the most common diagnosis was adjustment disorder(36.1%) comprising of anxiety and depressive symptoms owing to, in most cases, the antecedent mega earthquake of 2015.

**Table 4. Correlation of change in CSFQ-14 scores with dose of medication.**

Category	Mirtazapine		Sertraline	
	Dosage (19.34± 10.2mg)	P	Dosage (57.86± 14.5mg)	P
	Pearson Correlation		Pearson Correlation	
Pleasure	0.042	0.8	0.064	0.713
Desire (Frequency)	0.273	0.097	0.557	0.001*
Desire (Interest)	0.344	0.034	-0.009	0.96
Arousal	0.057	0.732	0.202	0.246
Orgasm	-0.163	0.328	0.197	0.257
Total CSFQ- 14 change	0.163	0.329	0.294	0.087

The mean doses of drug used in this study is lower than others<sup>8</sup> 19.34±10.26 for mirtazapine and 57.86±14.57 for sertraline partly because of a follow up period of just 4 weeks was used. Baseline CSFQ scores showed some level of sexual dysfunction despite excluding severe mental illness. This is explained by the fact that sexual dysfunction is already prevalent in “Normal” individuals<sup>14</sup> and those with anxiety disorders<sup>15</sup>. Also cultural factors may have influenced the finding.<sup>16</sup>

**Primary outcome:** After use of antidepressants, the Orgasm score after use of Sertraline was significantly lower than that of Mirtazapine (10.93±1.07 vs. 11.63±0.87; p=0.008). This is line with another study done by Montejo et al.<sup>8</sup> In Desire/Frequency subscale, clinically significant decline in scores in 13(34.2%) in mirtazapine and 9 (25.7%) in sertraline group and the difference was statistically significant (p=0.041). 5HT2c antagonism and sedation due to mirtazapine could be the likely causes. In the Orgasm aspect, significantly more patients showed problems with orgasm in the sertraline group than mirtazapine group (p=0.009). There was only weak correlation between drug dose and change in scores. The highest correlation was seen in dose of sertraline and decrease in Desire (Frequency) scores (r=0.557) and the result was statistically significant. (p=0.001). Also Dose of

mirtazapine showed some weak positive correlation with decrease in Desire (Interest) scores with statistical significance (r=0.344, p=0.034). This is in line with other studies<sup>17</sup>. The incidence of sertraline associated sexual dysfunction of 42.9% seen in this study is comparable to those in a study done by Clayton A et al.<sup>17</sup> and used the same but lesser than other studies<sup>8,18</sup>. In this study, incidence of mirtazapine associated sexual dysfunction(23.7%) was higher than what is generally expected and was comparable to the finding in the study by Montejo et al.<sup>8</sup> and clayton et al<sup>17</sup> but is contradicted in other studies.<sup>19,20,21</sup>

**CONCLUSION:**

The study attempts to evaluate the incidences of sexual dysfunction in patients receiving antidepressants in a Nepali population. The results of this study indicate that it is safer to assume that any antidepressant may be a cause of sexual dysfunction unless it is ruled out. Due to lower incidence of sexual dysfunction, some but not all patients with SSRIs induced sexual dysfunction, may benefit from switching to mirtazapine.

The results are based on a small population but they highlight the need of, and provide ground for, more systematic and controlled trials with larger population in the future

**ACKNOWLEDGEMENT: None**

**CONFLICT OF INTEREST: None**

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