

doi: <http://dx.doi.org/10.18203/2319-2003.ijbcp20150366>**Research Article****Adverse effects including sexual problems associated with the use of selective serotonin reuptake inhibitors in a tertiary care center of Eastern Nepal****Bhawesh Koirala^{1*}, Gajendra P. Rauniar¹, Dhana R. Shakya²**

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) use has been associated with various adverse drug events, including sexual problems in recent literature.

Methods: After written informed consent, remitted psychiatric patients were enrolled if they were taking an SSRI. The remitted state was ascertained by clinical assessment of a psychiatrist and reassessed with the use of self-response screening questionnaires (Beck Anxiety Inventory for anxiety, Beck Depression Inventory for depression). The self-response questionnaire “adverse drug effect (ADE) tool” was used to assess ADEs and the Arizona Sexual Experience Scale to assess sexual problems.

Results: The total of 200 subjects was enrolled with 63% females. Commonly used SSRIs were escitalopram, fluoxetine, and sertraline for the common diagnosis of depression, recurrent depressive disorder, and panic disorder in this institute. The average duration of remission during the enrollment was 11.99 months (standard deviation: 12.269). The overall prevalence of adverse effects was 91.5%. The incidence of adverse effect and sexual problem were: weight gain (57%), dryness of mouth (32.5%), headache (30%), dizziness (28.5%), paresthesia (24.5%), confusion (23.5%), tremors (21.5%), irritation (20.5%) sexual dysfunction (SD) (17.2%), increase in anxiety (17%), akathisia (16%), nausea (14.5%), itchiness (14.5%), excessive sweating, (14.5%), difficulty in sleeping (10%), weight loss (6%), rash (6%), diarrhea (4%), vomiting (3%), and others (3%).

Conclusion: Adverse effect (irrespective of severity) was commonly seen with SSRI use. Common adverse effects seen among remitted subjects were weight gain, dryness of mouth, headache, dizziness, paresthesia, etc. SD was other important side effect.

Keywords: Selective serotonin reuptake inhibitors, Adverse effects, Remitted psychiatric patients

INTRODUCTION

Adverse effects of drugs are unintended harmful effects of drugs. Almost every drug has its side effect or adverse effect along with its therapeutic effect. Antidepressant drugs are not different from other drugs. Older antidepressant drugs such as monoamine oxidase inhibitors and tricyclic antidepressants (TCAs) led to the development of significant, at times intolerable adverse effects that limited their use in clinical practice. Consequently, research efforts focused on developing drugs with similar efficacy, but with improved safety and tolerability profile. Many selective

serotonin reuptake inhibitors (SSRIs) introduced over the years are fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine. All of the SSRIs show a clear improvement in safety margin compared to the TCAs and are much safer in overdose. The improved tolerability of the SSRIs is attributable to their selectivity for the inhibition of SERT and to their absence of interaction with other receptors such as histaminic, cholinergic, dopaminergic, and noradrenergic. However, this does not mean that SSRIs are free of side effects. Serotonin receptors comprise at least seven classes that are further divided at the sub receptor level.

Excessive stimulation of brain 5-HT₂ receptors may result in insomnia, increased anxiety, irritability, decreased libido, and worsening of depressive symptoms. Excess activity at spinal 5-HT₂ receptors causes sexual side effects including erectile dysfunction, anorgasmia, and ejaculatory delay. Stimulation of 5-HT₃ receptors in the central nervous system and periphery contributes to gastrointestinal effects that are usually limited to nausea but may include diarrhea and emesis. Another common side effect of long-term SSRI therapy is weight gain. Although some SSRIs are typically associated with weight loss during initial therapy, weight is often regained after 6 months and followed by additional weight gain with long-term use. This hospital-based observational study is planned to find out the incidence of main adverse drug events of SSRIs with the use of Self Designed Adverse Effect Questionnaire and further find out the incidence of sexual problems, with the use of the "Arizona Sexual Experience Scale" (ASEX).

METHODS

Design: Hospital-based observational study

Setting: Outpatient clinic (outpatient department) of the Department of Psychiatry, BP Koirala Institute of Health Sciences (BPKIHS)

Subjects: Subjects consisted of 200 consecutive psychiatric patients who have remitted from acute phase and with continued SSRIs medications at least for 2 months

Sample size

Sample size was determined using formula:

$$N = 4pq/l^2$$

Where, p=Prevalence,

$$q = 100 - p$$

l = Permissible error (15% of p)

Taking 58% as p and adding non-responsive rate (10% of N), the sample size comes out to be 141. But prevalence in our setup is considered much lower, so sample size may be increased to 200 to improve the power of the study.

Duration of study: One year

Inclusion criteria

Those giving informed written consent. Consecutive patients, those who could respond, were in stable/remitted phase of psychiatric illness based on the assessment of a psychiatrist and aided by the assessment with Beck Anxiety Inventory and Beck Depression inventory (BAI and BDI) and are on SSRIs for at least 2 months of remission.

Exclusion criteria

Those who do not give a written informed consent and those who were physically unstable or in the active phase of mental illness.

Procedure

Written informed consent was taken from the subjects. Socio-demographic data were collected using semi-structured performa. The remitted state of the subject (from the indicated state of SSRI use, e.g., depression, anxiety) was declared upon the clinical assessment by a psychiatrist/consultant and it was reassessed with the use of self-responsescreening questionnaires BAI for anxiety, BDI for depression. The subjects were provided with self-response "adverse drug effect (ADE) tool" to assess ADEs and ASEX to access sexual problems. The responses were analyzed by following the instructions of the instruments.

Materials/instruments

1. Written informed consent from the authority
2. Semi-structured performa regarding socio-demographic profile
3. ADE questionnaire
4. ASEX
5. BAI
6. BDI.

ASEX

This tool was developed by the Department of Psychiatry and Psychology at the University of Arizona and Department of Psychiatry and Behavior Sciences, Stanford University, ASEX is a simple scale designed to measure five items identified as core elements of sexual function. These elements are sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm.

The items are rated on a six-point Likert scale ranging from 1 (hyperfunction) to 6 (hypofunction). The scale has two versions, one for males and one for females, with the difference in question 3 that refer penile erections versus vaginal lubrication. The scale is easy to compete, and the results may be used to assess current levels of sexual dysfunction (SD) or to monitor changes in SD over time following clinical interventions. The scale is useful in clinical trials to evaluate potential dysfunction caused by medications. In this scale a total score of more than 18 or three score of 4 (difficult) or a score of =>5 (very difficult) on any one item is associated with SD.

It has an excellent internal consistency, reliability, and validity. It is a self-rated scale and takes about 5-10 mins. It may be completed/rated by the interviewer. ASEX which has already been translated to Nepali and used in a previous study in BPKIHS¹ was applied in this study.

Self-designed ADE tools

This tool/questionnaire has been designed with the help of standard text books^{2,3,4} and relevant articles^{5,6} to extract common side effects of SSRIs considering its worldwide, regional and local literature and a global ADR assessment tool i.e. “The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale.” The 20 most common adverse effects of SSRIs were pooled from those books and articles and with reference to the UKU. The 20 most common side effects listed in this questionnaire are: insomnia, dizziness, increase in anxiety, nausea, vomiting, diarrhea, dryness of mouth, headache, tremors, rashes, pruritus, fatigue, weight gain, weight loss, excessive sweating, irritability, paresthesia, akathisia, and confusion. These items were compared with those of UKU side effect rating scale for the registration of unwanted effects of Psychotropics Manual English Version, October 1986 and were confirmed to be compatible by checking the items. Patients need to fill the box adjacent to each adverse effect with (√) if they have that particular problem and with (×) if they do not have that particular problem. The questionnaire is translated in Nepali for better understanding of the patients. The tool also has an “other” section that enables patients to express the side effect other than those listed in it.

BAI and BDI

BAI and BDI both created by Dr. Aaron T. Beck are 21 question multiple-choice self-report inventory used for measuring the severity of an individual’s anxiety and depression respectively. We are going to use these tools to find out remitted cases.

BAI and BDI translated in Nepali will be used in this study that have been adapted from one of the studies held in our institute itself each question in BAI has the same set of four possible answer choices, which are arranged in columns and are answered by marking the appropriate one with a cross.

These are:

- Not at all (0 points)
- Mildly: It did not bother me much (1 point)
- Moderately: It was very unpleasant, but I could stand it (2 points)
- Severely: I could barely stand it (3 points)

The BAI has a maximum score of 63.

- 0-7: Minimal level of anxiety
- 8-15: Mild anxiety
- 16-25: Moderate anxiety
- 26-63: Severe anxiety

We adopted the cutoff of 7 to ensure the remitted state from anxiety disorder that had been the cutoff in a previous study of BPKIHS.⁷ Similarly in BDI, each question has a set of at least four possible answer choices, ranging in intensity.

For example:

- (0) I do not feel sad
- (1) I feel sad
- (2) I am sad all the time, and I can’t snap out of it
- (3) I am so sad or unhappy that I can’t stand it.

When the test is scored, a value of 0-3 is assigned for each answer and then the total score is compared to a key to determine the depression’s severity. The standard cutoffs are as follows:

- 0-10: Normal
- 11-16: Indicates mild depression
- 17-20: Clinical borderline
- 21-30: Indicates moderate depression
- 31-40: Severe
- >40: Extreme.

Higher total scores indicate more severe depressive symptoms. We adopted the cutoff of 17.

Data processing

The coded performa was collected, and the information was entered into computer. The data were analyzed using software SPSS 18. The output of the study was able to provide data on incidence of adverse effect of SSRIs including sexual problems in remitted patients. Statistical measure-prevalence/incidence rate, mean and mode were calculated as per need. Comparison of the occurrence of adverse effects with in different SSRIs used was done by two-sided Chi-square test.

Ethical consideration

The study was done after obtaining the informed written consent from the subjects. Strict confidentiality of the information was maintained. The study was also approved by ethical committee of BPKIHS.

RESULTS

Most of the patients were from age group of 20 to 29 years (32.5%), followed by 30-39 years (30%). There were 15% patients from age group 40 to 49, 13.5% patients were below 20 years. About 9% patients were above 50 years of age of 200 patients, 126 (63%) were female and 74 (37%) were male. The majority of patients enrolled was married (78%). Most of the cases had the diagnosis of mood disorders of which 103 (51.5%) was depression and 26 (13%) had diagnosis of recurrent depressive disorder (RDD). Panic disorder was seen in 38 patients (19%) followed by anxiety not otherwise specified (NOS) 6.5%, obsessive compulsive disorder (OCD) 4.5%, generalized anxiety disorder (GAD) 4.5% (Figure 1). The average duration of remission during the enrollment was 11.99 months (standard deviation: 12.269). Most common drug used was escitalopram (43%), fluoxetine (30%), and sertraline (26%), and paroxetine was

used only in two patients (Figure 2). Commonly used dose of escitalopram was 10 mg that of fluoxetine was 20 mg and of sertraline was 50 mg. At least one adverse effect was present in 91.5% of the patients. Most common adverse effects were weight gain, dryness of mouth, headache dizziness, paresthesia, confusion, tremors, irritation, SD, and increase in anxiety (Figure 3).

There was no significant difference on the occurrence of other adverse effects with different drugs (Table 1). SD was seen in 17.2% (31) patients. Among them, 17 were female and 14 were male. The occurrence of decrease in sexual drive, difficulty in arousal and delayed orgasm with different drugs was somewhat similar. Decrease in sexual drive was seen in 24 patients (13.25%), 22 patients (12.15%) patients had delayed orgasm and 8.83% patients (16/181) was not satisfied with their orgasm. Decrease in sexual drive was commonly seen with fluoxetine 17.30% patients (9/52), followed by sertraline 13.40% (6/46) and escitalopram 11.11% (9/81). SD was commonly seen with fluoxetine, followed by escitalopram and sertraline.

DISCUSSION

Of 200 total patients, 126 (63%) were female and 74 (37%) were male. Women are more likely to be affected by socio-economic or physiological factors that may lead to their

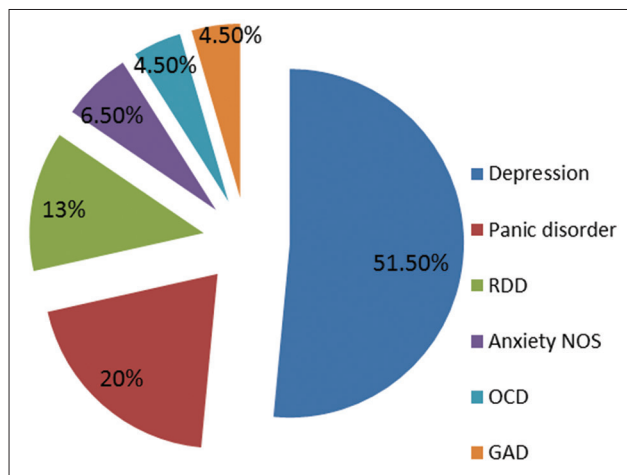


Figure 1: Diagnosis.

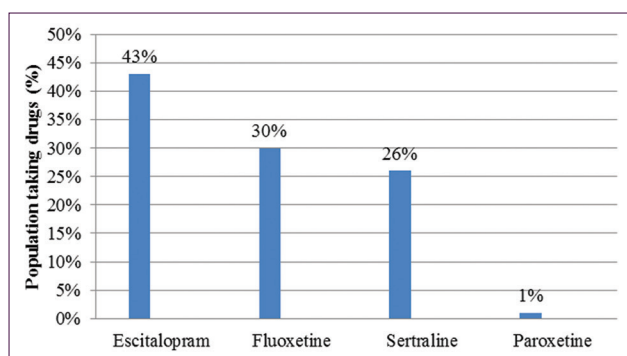


Figure 2: Drugs used.

using the medical system more than men. This may result in women being frequently diagnosed with medical problems such as depression or anxiety that are commonly addressed by prescribing drugs such as SSRIs. Cooperstock found that women are more likely than men to describe their problems in psychological or social terms and are therefore more likely to be diagnosed with psychoneurosis, anxiety or other instabilities.⁸

Most of the cases were of mood disorders of which 103 (51.5%) was depression, and 26 (13%) was case of RDD. 38 patients (19%) were of panic disorder followed by anxiety disorder NOS (6.5%), OCD (4.5%), and GAD (4.5%). This is similar to that seen in study done by Meijer et al.,⁹ in which most common diagnosis was depressive disorders, followed by anxiety disorders. The most common SSRI used was escitalopram, followed by fluoxetine and sertraline, respectively. Paroxetine was used only in two cases. This finding was consistent with finding of other recent studies that show escitalopram as most prescribed SSRI, followed by other drugs. In one expert review, it showed that escitalopram is at least as effective in the treatment of depression and anxiety as other SSRIs and may have cost-effectiveness and cost-utility advantages. Compared with other antidepressants, escitalopram is generally better tolerated, and its onset of action is relatively rapid. It seems to be an effective first-line option in the management of patients with major depression and various anxiety disorders. The overall prevalence of adverse effects was 91.5% that is relatively high. The previous studies showed prevalence of adverse up to 75%.¹⁰ In this study, the subjects had to respond "Yes" or No to the adverse effect items of the questionnaire irrespective of the severity. The higher prevalence seen in our study might be because of the fact that our study did not measure the severity of adverse effects. So, patient respond "Yes" to the questionnaire items even they had mildest form of the effects. Most of the patients were well tolerated to the drugs as they were remitted cases, and all were taking the drugs regularly. This shows that most of the patients even well-tolerated to SSRIs have one or other type of adverse effect, though might be present in the mildest of form. Extremely disparate incidence of SD has been found, varying between 1% and 96% although most of the data published pertain to short series reports from patients or to anecdote.¹¹⁻¹³ In another study, there was a significant increase in the incidence of SD when physicians asked the patients direct questions (58%) versus when SD was spontaneously reported (14%).¹⁴ In our study, SD was seen in 17.2% of patients. A retrospective study by Hsu and Shen¹⁵ showed that 30% of patients receiving SSRIs experienced sexual side effects. Another retrospective study found an overall rate of SD of 16%.¹⁶

Among various drugs, the incidence of SD was greatest in patients taking fluoxetine (21.50%), followed by escitalopram (16%) and sertraline (15%). A prospective study done by Jacobsen showed that 34% of patients receiving fluoxetine reported the onset of sexual side effects.¹⁷ The study done by Rosen et al. showed that estimates of the incidence of SD with fluoxetine have been

Table 1: Occurrence of adverse effects among different SSRIs (p value was calculated using Chi-square test).

Adverse effects	N (%)			p value
	Escitalopram (n=86)	Fluoxetine (n=60)	Sertraline (n=52)	
Weight gain (n=114)	54 (62.8)	33 (55)	25 (48)	0.23
Fatigue (n=87)	35 (40.69)	23 (38.3)	28 (53)	0.20
Dryness of mouth (n=65)	30 (34.9)	18 (30)	16 (30.8)	0.79
Headache (n=60)	21 (24.4)	21 (35)	18 (34.6)	0.28
Dizziness (n=57)	24 (27.9)	20 (33.3)	13 (25)	0.60
Paresthesia (n=49)	17 (19.8)	17 (28.3)	15 (28.8)	0.36
Confusion (n=47)	16 (18.6)	14 (23.3)	16 (30.8)	0.26
Tremors (n=43)	15 (17.4)	15 (25)	13 (25)	0.44
Irritation (n=41)	17 (19.8)	16 (26.7)	8 (15.4)	0.44
Increase in anxiety (n=34)	9 (10.5)	14 (23.3)	10 (19.2)	0.10
Akathisia (n=32)	10 (11.6)	13 (21.7)	9 (17.3)	0.26
Nausea (n=29)	13 (15.1)	8 (13.3)	8 (15.4)	0.94
Itchiness (n=29)	12 (14)	13 (21.7)	4 (7.7)	0.11
Excessive sweating (n=29)	13 (15.1)	8 (13.3)	8 (15.4)	0.94
Difficulty in sleep (n=20)	11 (12.8)	4 (6.7)	5 (9.6)	0.47
Weight loss (n=12)	2 (2.3)	3 (5)	7 (13.5)	0.027
Rash (n=12)	5 (5.81)	4 (6.66)	3 (5.76)	0.97
Diarrhea (n=8)	4 (4.7)	1 (1.7)	3 (5.8)	0.50
Vomiting (n=6)	2 (2.3)	3 (3.3)	2 (3.8)	0.86

SSRIs: Selective serotonin reuptake inhibitors

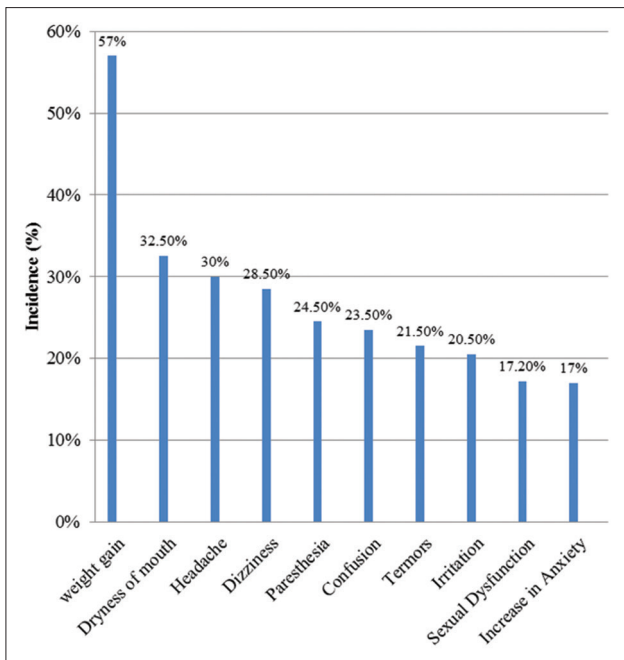


Figure 3: Most common side effects.

higher than initially thought. The incidence of adverse effects on sexual function with other SSRIs is not clear although clinical experience suggests that all SSRIs have the propensity to cause sexual side effects.¹⁸

Comparative studies of SSRIs have generally found no significant differences between drugs. For example, in a

prospective, multicenter, and descriptive clinical study of 344 patients, there was no statistically significant difference among different SSRIs used in the occurrence of different sexual side effects.¹⁴ Similarly in our study, there was no significant difference between different drugs in the occurrence of various sexual side effects.

CONCLUSION

Our study evaluated the prevalence of adverse effects among remitted psychiatric patients taking SSRIs via “ADE tool” and ASEX. From our study, it is revealed that the adverse effect (irrespective of severity) is common with SSRI use. Common adverse effects seen among remitted subjects are weight gain, dryness of mouth, headache, dizziness, paresthesia, etc. SD is other important side effect. There is no significant difference between different SSRIs in the occurrence of different adverse effects.

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