A naturalistic study on side effects of selective serotonin reuptake inhibitors in psychiatric out-patient department

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Abstract

Introduction:

Antidepressants are one of the most commonly prescribed psychotropic drugs. Six selective serotonin reuptake inhibitors are approved for various disorders. Selective serotonin reuptake inhibitors have fewer side effects owing to their selective blocking of the serotonin transporter. Nonetheless, selective serotonin reuptake inhibitors have several troublesome side effects, including nausea, diarrhea, headache, dizziness, sexual side effects, tachycardia and weight gain.

Methodology:

This cross-sectional comprised 200 participants who were divided into two groups. Group one had participants who had received selective serotonin reuptake inhibitors for less than six weeks duration and group two had participants who had taken selective serotonin reuptake inhibitors for more than six months. Side effects of medications were recorded using Udvalg for Kliniske Undersogelser side effect rating scale and causality was ascertained using Naranjo adverse drug reaction probability scale.

Results:

Among the early side effect group consisting of 100 participants, 40% of participants reported at least one side effect. Tension/inner unrest, nausea and vomiting, and orgasmic dysfunction was the most common side effect reported. 30% of participants in the late side effect group had at least one side effect. Orgasmic dysfunction, decreased sexual desire and weight gain were the main side effects reported. All the reported side effects were probably associated due to the prescribed selective serotonin reuptake inhibitors, as inferred from the Naranjo causality scoring system.

Conclusion:

Escitalopram was the most commonly prescribed selective serotonin reuptake inhibitor among all the selective serotonin reuptake inhibitors. Paroxetine and fluvoxamine were the least prescribed selective serotonin reuptake inhibitors. Sertraline was found to cause maximum side effects in the early group and fluoxetine caused the most side effects in the late group. Tension/Inner unrest was the most commonly reported side effect followed by sexual side effects.

Key words:
SSRI, anti-depressants, depression, side effects

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INTRODUCTION

Antidepressants are commonly prescribed psychotropic drugs. Amongst these, Selective Serotonin Reuptake Inhibitors (SSRIs) have rapidly emerged as well-tolerated, safe, and efficacious treatment options for depression, anxiety disorders, obsessive and compulsive disorders, and eating disorders. (1) Currently, six SSRIs are approved and are commonly used in routine clinical practice: citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and paroxetine.

SSRIs are better tolerated than earlier anti-depressants like tri-cyclic anti-depressants (TCA). SSRIs have fewer side effects due to the selective blocking of serotonin transporter (SERT) and sparing other neurotransmitter systems. (2) SSRIs cause side effects, including nausea, diarrhea, headache, dizziness, sexual side effects, tachycardia, and weight gain. (3) Rarely, they may also cause potentially life-threatening side effects, including gastrointestinal bleeding, hyponatremia, and serotonin syndrome. (4) Most of these side effects are a continuation of the serotonergic activity of SSRIs at different sites in the body.

SSRI increases the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell, thus increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. (5) (6) An adverse effect may be termed as a side effect when judged to be secondary to a main or therapeutic effect. (7) These are also the inevitable accompaniments of the medications and result in the dropout of participants. (8) Assess-

ment of side effects can be done by side effect checklists, semi-structured questionnaires, interviews, and rating scales. (9) Scales like General Assessment of Side Effects (10), Toronto Side Effect Rating Scale (11), Udvalg for Kliniske Undersogelser- Side Effect Rating Scale (UKU-SERS) (12), Systematic Assessment for Treatment Emergent Side Effects (13) can be used.

Current antidepressant drugs are effective and generally well tolerated. A study illustrates (8), the discontinuation rate as 25% owing to side effects. Another (14) study found nausea, diarrhea, headache, and agitation as the earliest side effect. Another noted gastrointestinal symptoms, weight gain, and metabolic abnormalities (15). A 2017 meta-analysis(16) concluded SSRI treatment does not lead to the development of autism spectrum disorder.

SSRIs can cause gastrointestinal bleeding and microvascular bleeding in the brain. Ischemic strokes are higher. (17) Arterial and venous thromboembolism have also been reported. (18) All SSRIs are associated with sexual side effects. It is highest with TCA's and MAOI, followed by SSRIs and venlafaxine, and lowest with bupropion and nefazodone. (19) SSRIs are frequently associated with delayed ejaculation, inability to ejaculate, and absent or delayed orgasm. Participants on SSRI have emotional blunting, irritability, sadness, and reduced motivation. SSRI-induced changes, including apathy, indifference, and reduced motivation, in children, adolescents, adults, and older adults are mentioned in the literature. (20)

The observation of a mildly increased risk of suicidal ideation on antidepressants in large clinical trials has resulted in intense debate about the role of antidepressant medication-induced activation in the initiation or worsening of suicidal ideation or behaviors. In 2003, the Medicines and Healthcare Products Regulatory Agency, the British counterpart of the FDA, banned the use of antidepressants, except fluoxetine, in children and adolescents.

Methodology

The current study is a cross-sectional study involving 200 males and females who were receiving at least one SSRI. The study was conducted in the out-participant department of psychiatry at All India Institute of Medical Sciences (AIIMS), New Delhi. One hundred participants on SSRI for less than 6 weeks (early side effects group or group 1 participants) and 100 participants on SSRI for more than 6 months (late side effects group or group 2 participants) were recruited for the study. This sample was taken on the basis of literature review of similar contemporary studies. Eligible participants were recruited between March 2017 to March 2018. Purposive sampling method was employed to recruit participants. Compliance to the SSRI's was ensured on the basis of information provided by the participants and their accompanying family members. 80% compliance to any SSRI was ensured using self-report and family-report. Eligible participants who met both the inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria for group 1 were participants between 18-50 years, of either gender receiving a single SSRI for 6 weeks or less, with adequate compliance and willingness to give written consent. Group 2 participants were 18-50 years, of either gender receiving a single SSRI for 6 months or more, with adequate compliance and willing to give written consent.

The exclusion criteria were diagnosis of seizure disorder, bipolar disorder, or psychotic disorder, clinical history of intellectual disability, history of co-morbid diabetes mellitus or hypertension, current or lifetime history of substance use disorder as per MINI 7.0 (except nicotine dependence), and participants who were on more than one antidepressant medication.

Participants meeting both inclusion and exclusion criteria were enrolled in the study. A socio-demographic proforma was used to collect the socio-demographic profile followed by a semi-structured clinical proforma for psychiatric history and treatment details. All the participants were screened using MINI (21) to confirm a diagnosis and rule out co-morbidities. Side effects of SSRI were systematically studied using the UKU side effects rating scale (22) and to ascertain causality Naranjo adverse drug reaction probability scale (23) was used.

The UKU side effect rating scale is a clinician rated scale used to assess the side effects of psychotropic medications. The UKU scale allows for a standardized evaluation of side effects, providing a systematic approach to monitoring and managing the adverse effects of psychotropic medications. The interpretation of UKU scale involves evaluating the severity and impact of side effects experienced by the patient. The scale uses a 4-point or 5-point rating system to assess each item, with the higher scores indicating greater severity or frequency of side effects.

The Naranjo adverse drug reaction probability scale consists of ten items that are used to assess the likelihood of an adverse drug reaction being caused by a specific medication. It provides a structured approach to rating the causality of adverse drug reactions, taking into account factors such as temporal relationship and alternative causes. Each item is scored on different point values (-1,0,+1 or +2), and the total score is used to categorize the

likelihood of the adverse drug reaction being caused by the medication, ranging from definite, probable, possible, to doubtful. Ethical clearance was sought from Institute Ethics Committee.

Descriptive statistics like percentages, and central tendencies were calculated and data were assessed for normal distribution. Inferential statistics in the form of group comparisons were done using Student's t-test, Mann Whitney U test, and Chi-Square test. The correlation was calculated using Pearson's correlation or Spearman's correlation as appropriate. The level of significance was considered as $p < 0.05$.

Results

Out of 293 participants, 93 (31.74%) participants were excluded because they didn't meet the inclusion/exclusion criteria required for the participation of the study. Of these ninety three patients, 13 patients were excluded as they were on two different SSRI at the time of assessment. Eight patients were excluded as they were on TCA along with a SSRI. Thirty two patients were on mood stabilizer along with a SSRI; hence they were also excluded from the study. Thirty nine patients were excluded as they were on antipsychotics along with SSRI. One patient did not give consent for the study hence excluded from the study. The total number of participants in Group 1 and Group 2 were 200, with 100 participants in each group. The details are provided in Table 1.

Table 1: Socio-demographic profile of participants of both groups

Socio-demographic variables		Early Side Effect Group (Group 1) (N=100)	Late Side Effect Group (Group 2) (N=100)
		N (%)	N (%)
Age (years); Mean (SD)		30.04 (8.63)	32.04 (8.70)
Gender	Male	64 (64%)	66 (66%)
	Female	36 (36%)	34 (34%)
Marital Status	Unmarried	35 (35%)	29 (29%)
	Married	63 (63%)	69 (69%)
	Divorced/Widowed/Separated	2 (2%)	2 (2%)
Education	Illiterate	4 (4%)	2 (2%)
	Up to 12th	63 (63%)	79 (79%)
	Above 12th	33 (33%)	19 (19%)
Occupation	Unemployed	11 (11%)	12 (12%)
	Housewife	23 (23%)	21 (21%)
	Student	26 (26%)	18 (18%)
	Business	12 (12%)	13 (13%)
	Other (Farmer/Professional/Retired)	28 (28%)	36 (36%)
Monthly Income (INR)	≤ 15,000	30 (30%)	42 (42%)
	>15,000	70 (70%)	58 (58%)
Religion	Hindu	81 (81%)	93 (93%)
	Muslim	14 (14%)	7 (7%)
	Others	5 (5%)	-

Clinical profile of participants

The mean duration of illness in group 1 was 3.09 ± 1.793 years while in group 2 was 4.77 ± 0.79 years. In group 1, 51% had Escitalopram as their SSRI prescription, followed by 22% Sertraline and 17% Fluoxetine. Also, 8% of the participants were taking Paroxetine and 2% were taking Fluvoxamine at the time of assessment. 78% of the participants who were taking one of the SSRIs had also benzodiazepine prescriptions in various dose ranges. Similarly, 16% of the participant had been prescribed beta-blocker. In group 2, 40% of participants had a prescription of Escitalopram, 25% had been using Sertraline, 26% Fluoxetine, 5% Paroxetine, and 4% was using Fluvoxamine. 35% of the participants were also prescribed a benzodiazepine and 17% were also on beta-blockers.

Overall, tab. Escitalopram was prescribed in the dose range of 2.5mg-30mg, tab. Sertraline from 25mg till 200mg, tab. Fluoxetine from 20mg-80mg, tab. Paroxetine from 12.5mg-37.5mg and tab. Fluvoxamine from 50mg-300mg. For group 1, the mean duration of treatment was 3.64 weeks. For group 2, the mean duration of treatment with SSRI medication was 16.74 months.

Socio-demographic co-relates

In order to assess if the two groups were comparable in regards to socio-demographic and clinical variables, bivariate analysis was conducted which are described in the table 2.

Table 2: Comparison of socio-demographic and clinical factors between early vs. late effect group.

Socio-demographic variables		Early Side Effect Group (Group 1) (N=100)	Late Side Effect Group (Group 1) (N=100)	Statistics[1] (p value)
		N (%)	N (%)	
Age (years); Mean (SD)[1]		30.04 (8.63)	32.04 (8.70)	-1.808 (0.070)
Gender	Male	64 (64%)	66 (66%)	0.087 (0.766)
	Female	36 (36%)	34 (34%)	
Marital Status	Unmarried	37 (37%)	31 (31%)	0.802 (0.370)
	Married	63 (63%)	69 (69%)	
Education	Up to 12th	67 (67%)	81 (81%)	5.0936 **(0.024)**
	Above 12th	33 (33%)	19 (19%)	
Monthly Income (INR)	≤ 15,000	30 (30%)	42 (42%)	3.125 (0.077)
	>15,000	70 (70%)	58 (58%)	
Religion	Hindu	81 (81%)	93 (93%)	6.366 **(0.011)**
	Muslim	14 (14%)	7 (7%)	
Duration of illness Mean (SD)		3.09 (1.793)	4.77 (0.79)	-6.36625 **(0.003)**
Duration of treatment Mean (SD)		3.64 (1.159)	16.74 (6.558)*	4.18919 **(0.002)**
Proportion of patients reporting any side effects		0.18	0.14	0.5952 (.440401)
Number of side effects		1.25	1.33	-4.356 **(0.008)**

1 Mann-Whitney U, Rest all other statistics calculated by Fischer's Exact test, *duration of treatment in months.

As per the Fischer Exact test, the distribution of data was

statistically correlated in education (p=0.024) and religion (p=0.011) among the socio-demographic profiles in the early and late side effect group. Similarly the distribution of data was also correlated in the duration of illness (p= 0.003), duration of time of treatment (p=0.002) and the number of reported side effects (p= 0.008) among the early and late side effect groups.

Side-effects of SSRI

Among group 1 participants 40% reported at least one side effect. The most frequently reported side effects along with causality of the mentioned side effects as devised from Naranjo probability scale are shown in below Table 3.

Table 3: Side effects reported by participants in the early side effect group (Group 1)

Side Effects (Acc. To UKU side effect rating scale)	Frequency (%)	Causality (Acc. To Naranjo adverse drug reaction probability scale)
Tension/inner unrest	18 (18%)	7 (probable causality)
Orgasmic dysfunction	11 (11%)	6 (probable causality)
Nausea/vomiting	10 (10%)	8 (probable causality)
Decreased sexual desire	9 (9%)	8 (probable causality)
Asthenia/lassitude/Increased fatigability	8 (8%)	7 (probable causality)
Increased duration of sleep	8 (8%)	8 (probable causality)
Erectile dysfunction	8 (8%)	8 (probable causality)
Ejaculatory dysfunction	8 (8%)	8 (probable causality)
Tension headache	8 (8%)	7 (probable causality)
Concentration difficulties	7 (7%)	6 (probable causality)

Among group 2 participants of 100 participants, 30% of participants reported at least one side effect. The side effects reported by the participants along with causality of the mentioned side effects as devised from Naranjo probability scale are tabulated and shown in below Table 4.

Table 4: Side effects reported by participants in the late side effect group (Group 2)

Side Effects (Acc. To UKU side effect rating scale)	Frequency (%)	Causality (Acc. To Naranjo adverse drug reaction probability scale)
Tension/inner unrest	14 (14%)	7 (probable causality)
Decreased sexual desire	13 (13%)	8 (probable causality)
Orgasmic dysfunction	13 (13%)	7 (probable causality)
Weight gain	11 (11%)	7 (probable causality)
Asthenia/lassitude/Increased fatigability	7 (7%)	6 (probable causality)
Erectile dysfunction	6 (6%)	7 (probable causality)
Concentration difficulties	5 (5%)	8 (probable causality)
Weight loss	5 (5%)	8 (probable causality)

Comparison of side effects of SSRI

In both groups' participants receiving SSRIs reported side effects. In group 1 tension/inner unrest was the most commonly reported side effect followed by orgasmic dysfunction. In group 2 orgasmic dysfunction and decreased sexual desire were the most common reported side effects. The commonly reported side effects by the participants who were taking medication for the short term (<6 weeks) and those taking SSRIs for the long term (>6 months) are tabulated in Table 5. In order to assess if the two groups were comparable in regards to side effect profile, bivariate analysis was conducted which is also described in the table 5. Only the five most common symptoms were considered for statistical analysis as the sample size for other side effects were less for subgroup analysis. Out of the five reported symptoms only nausea/vomiting was significantly different between the early and late side effects group (p=0.0446).

Table 5: Comparison of reported side effects between the Early group (N=100) and Late group (N=100)

Side effect	Early Side Effect Group (Group 1), N (%)	Late Side Effect Group (Group 2), N (%)	Statistics* (p Value)
Tension/inner unrest	18 (18%)	14 (14%)	0.595 (0.440)
Orgastic dysfunction	11 (11%)	13 (13%)	0.189 (0.663)
Nausea/vomiting	10 (10%)	3 (3%)	4.031 (0.0446)
Decreased sexual desire	9 (9%)	13 (13%)	0.817 (0. 366)
Weight gain	5 (5%)	11 (11%)	2.445 (0.117)

Similarly, the side effects reported were also different for different SSRIs in both groups. Table 6 highlights the most commonly reported side effects by SSRI prescription pattern in both the early and late side effect groups.

Table 6: Most commonly reported side effects (Early vs. Late) by different SSRIs

SSRI	Early Side Effect Group (Group 1)			Late Side Effect Group (Group 2)		
	Frequency (%) of Prescription	Percentage (%) of side effects amongst the participants prescribed the particular drug*	Reported the commonest side effect	Frequency (%) of Prescription	Percentage (%) of side effects amongst the participants prescribed the particular drug*	Reported the commonest side effect
Escitalopram	51%	41.17%	Tension/inner unrest Erectile dysfunction Ejaculatory dysfunction Orgasmic dysfunction Nausea/vomiting	40%	25.0%	Decreased sexual desire Orgasmic dysfunction Erectile dysfunction Tension/inner unrest
Sertraline	22%	50%	Tension/inner unrest Palpitations/ tachycardia Nausea/vomiting Orgasmic dysfunction	25%	24%	Orgasmic dysfunction Decreased sexual desire Weight gain Tension/inner unrest
Fluoxetine	17%	47.05%	Concentration difficulties Tension/ inner unrest Increased duration of sleep Orgasmic dysfunction	26%	34.61%	Decreased sexual desire Orgasmic dysfunction Tension/inner unrest Asthenia/lassitude/ Increased fatigability
Paroxetine	8%	–	–	5%	60%	Weight gain Tension/ inner unrest Orgasmic dysfunction Ejaculatory dysfunction
Fluvoxamine	2%	–	–	4%	50%	Tension/inner unrest Orgasmic dysfunction Decreased sexual desire Weight gain

Discussion

The present study aimed at assessing the early and late side effects of SSRIs using a standardized scale and also assesses the causality of that side effect with the prescribed SSRI. Escitalopram was the most commonly prescribed SSRI among all the SSRIs. Sertraline was found to cause the maximum number of side effects in the early group. Fluoxetine caused the most side effects in the late group. Tension/Inner unrest was the most commonly reported side effect followed by sexual side effects in both the early and late side effect group. All the reported side effects were probably associated due to the prescribed SSRI, as inferred from the Naranjo causality scoring system.

Early Side Effect Group

Among the early side effect group consisting of 100 participants, 40% reported at least one side effect. The most common reported side effect was tension/inner followed by orgasmic dysfunction and nausea/vomiting. Similar side effects were seen in contemporary Indian studies where the SSRIs showed more psychiatric adverse drug reactions like agitation, nervousness, and anxiety. (24)

Sertraline has been seen in studies to cause more gastrointestinal side effects during the initial weeks of the start of treatment. It has also been shown to cause withdrawals after abrupt cessation. (25) Participants receiving paroxetine in the early side effect group did not report any side effects. Although it has been shown from the literature that paroxetine causes more sedation as compared to other SSRIs and is also responsible for withdrawal symptoms after abrupt cessation. (25)

Late Side Effect Group

Among 100 participants, 30% reported at least one side effect. The most common side effect reported was tension/inner unrest followed by decreased sexual desire and orgasmic dysfunction. This was followed by weight gain. Some studies also mention weight gain and sexual side effects as the most common side effects after prolonged treatment from SSRI. (25) The higher reporting of sexual side effects in participants prescribed SSRI for a long duration has been well documented in the literature. (26) (27)

Chronic fluoxetine treatment (26) was associated with symptoms of restlessness, tension, agitation, and sleep disturbances. Weight gain was reported as a major side effect of paroxetine. (25) Paroxetine can also cause sedation, constipation, sexual dysfunction, discontinuation syndrome, and weight gain. (28)

Comparison of side effects of SSRI

In both groups' participants receiving SSRIs reported side effects. Although tension/inner unrest remained the most commonly reported side effect, the frequency of other side effects varied. In the early side effect group, orgasmic dysfunction was the second most commonly reported side effect followed by nausea and vomiting. In the late side effect group, orgasmic dysfunction and decreased sexual desire were the two second most common reported side effects followed by weight gain.

In both the group frequency of sexual side effect was more than tension/inner unrest as both orgasmic dysfunction and decreased sexual desire are the components of sexual side effects. Overall, escitalopram appears to be the best-tolerated SSRI, followed by fluoxetine, sertraline, paroxetine, and fluvoxamine. The latter two drugs are associated with the most side effects and the highest discontinuation rates because of side effects in clinical trials. (29) During long-term SSRI therapy, the most troubling adverse effects are sexual dysfunction, weight gain, and sleep disturbance.

Contemporary study also lists common side effects of SSRI as was highlighted in our study including nausea/vomiting, decreased sexual drive and agitation. The same study also lists some rare side effects like extrapyramidal symptoms, serotonin syndrome, rash and birth defects which was not noted in any of our participants. This may be because of the mean age of our participants being 30 years. (30)

In a different large scale study the commonly noted side effects were related to sleep, eating pattern, weight gain and sexual desires. Our participants had uneasiness/unrest and sexual side effects on both the groups. There were a minor group of participants who was found to have difficulties with sleeping but none had reported any difficulty with eating patterns.(31)

Strengths of the study

The following study, to the best of our knowledge, is one its kind in the Indian population to systematically study the early and late side effects of SSRI using a standardized scale along with the assessment of causality using the Naranjo Adverse Drug Reaction Probability Scale. Large sample size in both the study groups which is representative of North Indian population. Inclusion criteria were made robust so that the participant included were only taking one SSRI at the time of assessment.

Limitations of the study

The study was cross-sectional and hence follow-up was not done to monitor the persistence of the side effects. Participants who were prescribed benzodiazepine and beta-blockers were included in the study. The perceived side effects could also be the manifestations of the above medications. However, these side effects have been tried to eliminate using the adverse drug reaction probability scale. Only the side effects mentioned in the UKU Side Effect Rating Scale were taken into consideration. Off-label side effects were not reported by the participants and hence were not included in the study group. Participants receiving paroxetine and fluvoxamine were fewer in our study hence; the reported side effects cannot be generalized to these participants.

Conclusion

The groups were comparable on socio-demographic parameters like age, gender, marital status, education, occupation, monthly income, and religion. They also were comparable in their total duration of illness. In both groups, escitalopram was the most prescribed SSRI. In the late side effect group, fluoxetine had a slightly higher prescription pattern.

Escitalopram was the most commonly prescribed SSRI among all the SSRIs. The frequency of prescription of fluoxetine and sertraline was similar. Paroxetine and fluvoxamine were the least prescribed SSRIs. Comparatively, sertraline was found to cause the maximum number of side effects in the early group and fluoxetine caused the most side effects in the late group. Sexual side effects was the most commonly reported side effect followed by tension/inner unrest in both the early and late side effect group. All the reported side effects were probably associated due to the prescribed SSRI, as inferred from the Naranjo causality scoring system.

It would be advisable to conduct studies with larger sample sizes and possibly multicentric to look for increased generalizability of the results. The prospective design needs to be implemented to establish the side effect profile. Awareness should be created among the physicians as well as the paramedical staff regarding the various adverse drug reactions which are caused by antidepressants so that morbidity can be reduced.

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Declaration of Conflict of Interests

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