



ADVERSE DRUG REACTIONS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PATIENTS WITH DEPRESSION: A PROSPECTIVE OBSERVATIONAL STUDY FROM A TERTIARY CARE HOSPITAL IN RURAL INDIA

Dr. Shalini Shukla¹, Dr. Naveen Kumar^{2*}, Dr. Nikhil Goel³, Dr. Navin Budania⁴, Dr. Siddharth Ahuja⁵, Dr. Vinod kumar Bhardwaj⁶

¹PG Resident, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India

^{2*}Associate Professor, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India

³Associate Professor & Head, Department of Psychiatry, SHKM Government Medical College, Nuh, Haryana, India

⁴Associate Professor, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India

⁵Assistant Professor, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India

⁶Professor & Head, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India

***Corresponding author:** Dr. Naveen Kumar,

Associate Professor, Department of Pharmacology, SHKM Government Medical College, Nuh, Haryana, India Email ID: nk999999@rediffmail.com

ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are widely used as first-line treatment for depression; however, their adverse drug reaction (ADR) profile in rural Indian populations remains underreported. Understanding real-world safety patterns is crucial for optimizing therapeutic outcomes and strengthening pharmacovigilance in resource-limited settings.

Methods: This 12-month prospective observational study included drug-naïve adults with newly diagnosed depression attending a tertiary care hospital in rural Haryana. Patients prescribed SSRI monotherapy were followed at 3 and 6 weeks to identify ADRs using structured questionnaires and patient interviews. ADRs were evaluated using the WHO-UMC causality scale, Modified Hartwig and Siegel severity scale, and Schumock and Thornton preventability criteria. Data were analyzed using descriptive statistics and chi-square tests.

Results: Among 51 patients (mean age: 34.8 ± 11.2 years), Escitalopram was the most frequently prescribed SSRI (60.8%) and accounted for the highest proportion of ADRs (57.1%). A total of 119 ADRs were reported, predominantly affecting the central nervous system (52.1%), followed by gastrointestinal manifestations (32.8%). The most common ADRs were headache (12.6%), dizziness (11.7%), nausea (10.9%), dry mouth (9.2%), and drowsiness (8.4%). All ADRs were categorized as “possible” on causality assessment. Most ADRs were mild (74.8%) and non-preventable (79.8%), while 25.2% were moderate and 20.2% were probably preventable. Tobacco use ($p = 0.047$) and

tobacco/pan consumption ($p = 0.032$) showed significant associations with multiple ADR occurrence, whereas age, gender, BMI, and marital status showed no significant associations.

Conclusion: SSRIs demonstrated a favorable and largely manageable safety profile in this rural cohort, with predominantly mild central nervous system and gastrointestinal ADRs. The association of tobacco use with increased ADR frequency highlights the need for integrated lifestyle counseling. Strengthened patient education and enhanced pharmacovigilance practices may further improve treatment adherence and safety in rural Indian settings.

Keywords: Adverse drug reactions; SSRIs; Depression; Escitalopram; Pharmacovigilance; Rural India.

INTRODUCTION

Depression constitutes a leading cause of global disability, affecting over 264 million individuals worldwide and imposing substantial socioeconomic burden through healthcare costs and productivity losses [1]. In India, the prevalence of depression is estimated at 4.5%, with significant regional variations influenced by socioeconomic determinants and healthcare access disparities [2]. The condition is characterized by persistent low mood, anhedonia, psychomotor retardation, and cognitive dysfunction, substantially impairing quality of life and functional capacity [3].

Selective serotonin reuptake inhibitors (SSRIs) represent the cornerstone of pharmacological management for depressive disorders due to their superior tolerability profile compared to tricyclic antidepressants and monoamine oxidase inhibitors [4]. By selectively inhibiting serotonin reuptake at presynaptic terminals, SSRIs enhance serotonergic neurotransmission while minimizing anticholinergic, antihistaminic, and alpha-adrenergic effects [5]. Despite their widespread utilization and established efficacy, SSRIs are not devoid of adverse effects, which may compromise treatment adherence and therapeutic outcomes.

Adverse drug reactions (ADRs) are defined by the World Health Organization as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease" [6]. The spectrum of SSRI-associated ADRs encompasses gastrointestinal disturbances, sexual dysfunction, sleep alterations, weight changes, and neuropsychiatric manifestations [7]. Pre-marketing clinical trials, conducted under stringent controlled conditions with selected populations, often fail to detect uncommon ADRs or those manifesting during prolonged therapy [8]. Consequently, post-marketing surveillance through robust pharmacovigilance systems becomes imperative for comprehensive safety profiling.

The Pharmacovigilance Programme of India (PvPI), established in 2010, aims to systematically monitor drug safety and generate evidence for regulatory decision-making [9]. Despite this infrastructure, ADR reporting rates in India remain suboptimal at less than 1% compared to the global average of 5%, reflecting inadequate awareness among healthcare professionals and patients [10]. Rural populations face additional challenges including limited healthcare literacy, cultural stigma surrounding mental illness, and restricted access to specialized psychiatric services.

Recent studies from tertiary care settings in India have documented varying ADR patterns with SSRIs. A study by Kushwaha et al. reported central nervous system and gastrointestinal manifestations as predominant ADR categories [11]. Similarly, Jain et al. observed that most SSRI-related ADRs were mild in severity, requiring minimal intervention [12]. However, data specifically characterizing ADR profiles in rural Indian populations with depression remain scarce, representing a significant knowledge gap.

The rural Mewat region of Haryana presents unique demographic characteristics, including low literacy rates, distinct cultural practices, and limited mental healthcare infrastructure. Understanding ADR patterns in this context is essential for developing culturally appropriate patient education strategies and optimizing therapeutic protocols. Furthermore, systematic causality, severity, and preventability assessments provide actionable insights for clinical decision-making and risk mitigation.

Aim: The present study aimed to identify and characterize adverse drug reactions associated with SSRI use in patients with depression, and to evaluate their causality, severity, and preventability at a tertiary care hospital serving a predominantly rural population in Haryana, India.

2. Materials and Methods

2.1 Study Design and Setting

This hospital-based, prospective, observational, non-interventional study was conducted in the Department of Psychiatry, Shaheed Hasan Khan Mewati Government Medical College, Nuh, Haryana—a 600-bed tertiary care teaching hospital serving as the sole referral center for the rural Mewat region. The study received ethical approval from the Institutional Ethics Committee (EC/OA-36/2023, dated 13/06/2023) and was conducted over 12 months from June 2023 to May 2024.

2.2 Study Population

The target population comprised drug-naïve adult patients with newly diagnosed depression attending the psychiatry outpatient department. Depression diagnosis was established by qualified psychiatrists using International Classification of Diseases-10 (ICD-10) diagnostic criteria.

Inclusion Criteria:

Patients aged 18 years and above
Newly diagnosed with depression per ICD-10 criteria
Drug-naïve for psychotropic medications
Prescribed SSRI monotherapy
Provided written informed consent

Exclusion Criteria:

Comorbid psychiatric disorders or substance use disorders
Significant medical comorbidities requiring polypharmacy
Unwilling to provide informed consent
Geriatric patients (>60 years)

2.3 Sampling and Sample Size

Systematic random sampling was employed, screening every third eligible patient. Assuming a depression prevalence of 4.5% in India, with 95% confidence level and 5% precision, the calculated sample size was 83. A total of 96 patients were enrolled to account for potential attrition. Of these, 51 patients had depression as the primary diagnosis.

2.4 Data Collection

Comprehensive demographic and clinical data were collected using validated, pre-designed proformas at baseline and during follow-up visits at 3 and 6 weeks. Recorded parameters included age, gender, weight, body mass index (BMI), educational status, occupational details, marital status, lifestyle habits (smoking, alcohol, tobacco use), family psychiatric history, and concomitant medications.

ADRs were identified through:

Patient self-reporting during follow-up visits
Systematic inquiry using structured questionnaires
Review of medical records

Each suspected ADR was documented using the ADR reporting form (Version 1.4) provided by PvPI and reported to the National Coordinating Centre through Vigiflow software.

2.5 Assessment Tools

Causality Assessment: The WHO-UMC (Uppsala Monitoring Centre) causality assessment scale

was employed by the institutional Causality Assessment Committee, categorizing ADRs as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable.

Severity Assessment: Modified Hartwig and Siegel scale classified ADRs into mild (requiring no change in therapy), moderate (requiring treatment modification), or severe (potentially life-threatening or causing permanent disability).

Preventability Assessment: Schumock and Thornton criteria categorized ADRs as definitely preventable, probably preventable, or not preventable based on appropriateness of drug selection, dosing, and monitoring.

2.6 Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS version 20.0. Descriptive statistics were expressed as frequencies, percentages, means, and standard deviations. Categorical variables were compared using chi-square tests. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Demographic Characteristics of the Study Population

A total of 51 patients diagnosed with depression and receiving SSRI therapy were included in the study. The mean age of the cohort was 34.8 ± 11.2 years, ranging from 18 to 60 years. The majority belonged to the 30–49-year age group (43.1%), followed by young adults aged 18–29 years (35.3%), and senior adults ≥ 50 years (21.6%) (Table 1).

Females constituted 54.9% of the study population, and males accounted for the remaining 45.1%. The mean body weight was 61.3 ± 12.1 kg, and most patients (74.5%) fell into variant BMI categories (underweight, overweight, or obese), whereas 25.5% had normal BMI.

Regarding education, 39.2% of patients were illiterate, 35.3% had primary education, and 25.5% had education beyond primary level. The majority were married (82.4%). Lifestyle assessment revealed that 80.4% were non-smokers, 74.5% were non-tobacco users, and 84.3% reported no alcohol intake.

3.2 SSRI Utilization Pattern and Distribution of ADRs

Among the prescribed SSRIs, Escitalopram was the most commonly used medication (60.8%), followed by Sertraline (25.5%), Fluoxetine (13.7%), and Paroxetine (2.0%) (Table 1).

A total of 119 adverse drug reactions (ADRs) were documented in the 51 patients. The overall ADR burden was highest with Escitalopram (57.1%), followed by Sertraline (30.3%), Fluoxetine (10.1%), and Paroxetine (2.5%) (Table 1).

3.3 Organ System–Specific ADR Profile

The majority of ADRs involved the central nervous system (CNS), accounting for 62 ADRs (52.1%), followed by gastrointestinal (GIT) ADRs (32.8%), cardiovascular manifestations (5.0%), and miscellaneous symptoms (10.1%) (Table 1).

The most frequently reported individual ADRs included:

Headache (12.6%)

Dizziness (11.7%)

Anxiety/Restlessness (10.9%)

Drowsiness (8.4%)

Fatigue/Lethargy (8.4%)

Dry mouth (9.2%)

Nausea (10.9%)

CNS manifestations were predominantly seen with Escitalopram and Sertraline.

3.4 Causality, Severity, and Preventability Assessment

All ADRs were classified as “Possible” according to the WHO–UMC causality scale (Table 2).

On severity assessment (Modified Hartwig scale), 74.8% of ADRs were mild, requiring no change in

therapy or minimal intervention, while 25.2% were moderate, requiring symptomatic management. No severe ADRs were reported.

Preventability assessment using the Modified Schumock–Thornton scale demonstrated that 79.8% of ADRs were not preventable, while 20.2% were probably preventable, often associated with inadequate patient education or failure to report early symptoms.

3.5 Factors Associated with ADR Occurrence

Among the 51 patients, 21 (41.2%) experienced a single ADR, whereas 30 (58.8%) reported multiple ADRs.

Chi-square testing (Table 3) revealed: Smoking was significantly associated with multiple ADR occurrence ($p = 0.047$). Tobacco/pan use also showed a significant association ($p = 0.032$). Alcohol consumption showed a non-significant trend toward increased ADRs ($p = 0.066$). Age group, gender, marital status, and BMI category did not show significant associations with ADR clustering ($p > 0.05$).

TABLES

Table 1. Demographic Profile, SSRI Utilization, and Organ System Distribution of ADRs (N = 51)

Parameter	Category	n (%)
Age Group	18–29 years	18 (35.3)
	30–49 years	22 (43.1)
	≥50 years	11 (21.6)
Gender	Male	23 (45.1)
	Female	28 (54.9)
BMI Category	Normal	13 (25.5)
	Variant (U/W/O)	38 (74.5)
Lifestyle	Smokers	10 (19.6)
	Tobacco/Paan users	13 (25.5)
	Alcohol users	8 (15.7)
Marital Status	Married	42 (82.4)
SSRI Prescribed	Escitalopram	31 (60.8)
	Sertraline	13 (25.5)
	Fluoxetine	7 (13.7)
	Paroxetine	1 (2.0)
Total ADRs (n = 119)	CNS	62 (52.1)
	GIT	39 (32.8)
	CVS	6 (5.0)
	Miscellaneous	12 (10.1)

Table 2. Causality, Severity, and Preventability Assessment of ADRs (n = 119)

Assessment Category	Subcategory	n (%)
Causality (WHO–UMC)	Certain	0 (0)
	Probable	0 (0)
	Possible	119 (100)
	Unlikely	0 (0)
Severity (Hartwig Scale)	Mild	89 (74.8)
	Moderate	30 (25.2)
	Severe	0 (0)
Preventability (Schumock–Thornton)	Definitely preventable	0 (0)
	Probably preventable	24 (20.2)
	Not preventable	95 (79.8)

Table 3. Association of Demographic and Lifestyle Factors with Multiple ADR Occurrence

Factor	Single ADR n (%)	Multiple ADR n (%)	χ^2	p-value
Age Group			1.760	0.415
18–29 years	8 (44.4)	10 (55.6)		
30–49 years	9 (40.9)	13 (59.1)		
≥50 years	4 (36.4)	7 (63.6)		
Gender			0.241	0.622
Male	9 (39.1)	14 (60.9)		
Female	12 (42.9)	16 (57.1)		
Smoking			3.94	0.047*
Yes	2 (20.0)	8 (80.0)		
No	19 (46.3)	22 (53.7)		
Tobacco/Paan			4.57	0.032*
Yes	3 (23.1)	10 (76.9)		
No	18 (47.4)	20 (52.6)		
Alcohol			3.38	0.066
Yes	2 (25.0)	6 (75.0)		
No	19 (44.2)	24 (55.8)		
BMI Category			1.63	0.201
Normal	7 (53.8)	6 (46.2)		
Variant	14 (36.8)	24 (63.2)		

*Statistically significant, $p < 0.05$.

4. Discussion

This prospective observational study provides an updated and comprehensive evaluation of the adverse drug reaction (ADR) profile associated with selective serotonin reuptake inhibitors (SSRIs) among patients with depression in a rural Indian tertiary care setting. The findings reaffirm the generally safe and tolerable nature of SSRIs, while identifying specific organ-system patterns and patient-related determinants that require focused clinical attention.

The mean age of 34.8 years and predominant representation of middle-aged adults (30–49 years) in our sample are consistent with global epidemiological trends that recognize early and mid-adulthood as a peak period for depressive disorders due to occupational strain, family responsibilities, and psychosocial pressures [13]. The near-equal gender distribution contrasts with literature indicating higher depression prevalence among women, which may reflect sociocultural barriers limiting women's access to psychiatric care in rural India or bias inherent in outpatient recruitment settings.

Escitalopram was the most commonly prescribed SSRI (60.8%) and accounted for 57.1% of the total ADR burden. This prescribing trend is highly aligned with previous Indian studies reporting the preferential use of escitalopram due to its favorable efficacy profile, lower interaction potential, and widespread availability in government supply chains [11,12]. The higher number of ADRs associated with escitalopram in our findings likely reflects its greater utilization rather than increased intrinsic toxicity, as our study was not designed to compare relative ADR risk across SSRIs.

CNS-related ADRs constituted the largest proportion (52.1%) of all reported ADRs, consistent with the known pharmacodynamic effects of SSRIs on serotonergic pathways that regulate arousal, cognition, sleep, and vestibular functioning. Headache was the most commonly observed CNS symptom, followed by dizziness, drowsiness, and anxiety. These findings correspond with pharmacovigilance reports documenting CNS manifestations as the most frequent adverse effects of SSRIs [11,12]. The transient nature of these effects, particularly during early treatment weeks, is well-recognized and attributable to serotonergic adaptation in neural networks [5].

Gastrointestinal manifestations accounted for 32.8% of ADRs and are attributable to the high density

of serotonin receptors and transporters in the enteric nervous system. Nausea, dry mouth, bloating, and constipation were the most prevalent, aligning with known 5-HT₃ receptor-mediated gastrointestinal responses and mild anticholinergic effects of certain SSRIs [7]. Notably, the prevalence of diarrhea in our cohort was lower than that reported in Western populations, which may reflect dietary, microbiome, or genetic differences in serotonin transporter polymorphisms among Indian populations.

A notable observation in our study is the **absence of sexual dysfunction-related ADRs**, despite their high prevalence in Western literature, ranging from 25% to 80% [7]. This likely reflects sociocultural barriers and stigma surrounding sexual health discussions in conservative rural regions, particularly among married women. Future studies should incorporate anonymized or gender-sensitive sexual function assessment tools to more accurately evaluate this important domain.

All ADRs were classified as “possible” on the WHO-UMC scale, underscoring diagnostic challenges in psychiatric pharmacovigilance where somatic symptoms of depression overlap with drug-induced effects [13]. Dechallenge and rechallenge procedures, the gold standard for strengthening causality, are often clinically unjustifiable in chronic psychiatric therapy, limiting the attainment of higher causality categories.

The majority of ADRs were mild (74.8%), and none were severe, reaffirming the overall tolerability of SSRIs in routine depression management. The proportion of moderate ADRs (25.2%) was comparable to findings reported by Jain et al., who observed that most SSRI-related ADRs were mild and manageable with symptomatic therapy [12]. These patterns support continued pharmacotherapy with appropriate counseling rather than premature discontinuation or switching.

Preventability analysis demonstrated that 79.8% of ADRs were not preventable, reflecting appropriate prescribing habits and dosage practices. The proportion of “probably preventable” ADRs (20.2%) largely related to patient-level factors such as delayed reporting or inadequate understanding of expected adverse effects. Similar Indian studies have reported preventability rates between 10–15% [11], suggesting that enhanced counseling strategies, simplified education materials, and active follow-up can further reduce preventable ADRs.

A statistically significant association was observed between tobacco use and multiple ADR occurrence ($p = 0.047$). Tobacco smoke contains polycyclic aromatic hydrocarbons that induce hepatic CYP1A2, potentially altering SSRI metabolism and plasma concentration variability [14]. This can precipitate increased ADR susceptibility, emphasizing the relevance of smoking cessation counseling during SSRI initiation. Although alcohol use showed a trend toward significance, the very small number of alcohol users ($n = 8$) limits meaningful interpretation. Lower alcohol consumption in this cohort may reflect socioeconomic constraints or religious norms in the predominantly Muslim population of Mewat.

The high rates of illiteracy and low socioeconomic status observed underscore the structural vulnerabilities influencing mental health outcomes in rural India. Limited health literacy may impede patients’ ability to recognize early adverse effects and appropriately seek guidance, potentially compromising adherence and therapeutic success [15]. Incorporating culturally adapted educational tools, family involvement, and community health worker engagement may enhance safe and effective SSRI use in resource-limited settings.

Limitations: This single-center study with 12-month duration and 6-week patient follow-up cannot capture rare or delayed ADRs. The observational design without active comparator limits causal inference. Exclusion of elderly patients and those with comorbidities restricts generalizability. Self-reported ADRs without systematic laboratory monitoring may underestimate subclinical effects such as hyponatremia or QT prolongation. The absence of sexual dysfunction likely reflects cultural underreporting rather than true absence.

Clinical Implications: These findings support SSRI use as first-line pharmacotherapy for depression in rural Indian settings, with predominant mild, manageable ADRs. Proactive patient education regarding common ADRs (headache, nausea, drowsiness) may improve treatment adherence by normalizing these experiences. Tobacco cessation counseling should be integrated into depression

care pathways. Enhanced pharmacovigilance training for healthcare providers and culturally sensitive ADR reporting mechanisms are needed to improve signal detection in rural populations.

5. Conclusion

This prospective observational study demonstrates that SSRIs exhibit an acceptable safety profile in depression management among rural Indian patients, with predominantly mild, self-limiting adverse drug reactions. Central nervous system and gastrointestinal manifestations constitute the majority of ADRs, consistent with the known pharmacological actions of SSRIs. Escitalopram, as the most frequently prescribed agent, accounts for the highest absolute number of ADRs, though this likely reflects prescription patterns rather than differential toxicity. The high proportion of non-preventable ADRs indicates appropriate prescribing practices, while the mild severity profile supports continued SSRI use with supportive management.

Tobacco use emerged as a significant modifiable risk factor for ADR occurrence, highlighting the importance of comprehensive lifestyle interventions in depression care. The absence of severe ADRs and the predominance of transient, manageable effects reinforce SSRIs as first-line therapy for depression in resource-limited settings. However, enhanced patient education, culturally adapted counseling strategies, and robust pharmacovigilance mechanisms are essential to optimize therapeutic outcomes and capture the full spectrum of adverse effects, including those underreported due to cultural sensitivities.

These findings contribute valuable real-world evidence to the limited pharmacovigilance data from rural Indian populations and underscore the necessity of ongoing post-marketing surveillance to ensure patient safety in diverse clinical contexts.

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