



ADVERSE DRUG REACTIONS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN GENERALIZED ANXIETY DISORDER: A PROSPECTIVE OBSERVATIONAL STUDY FROM A TERTIARY CARE HOSPITAL IN RURAL INDIA

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ABSTRACT

Background: Generalized anxiety disorder (GAD) affects approximately 6% of the population globally, with selective serotonin reuptake inhibitors (SSRIs) representing first-line pharmacotherapy. However, adverse drug reaction (ADR) profiles in real-world settings, particularly in rural Indian populations with GAD, remain inadequately documented.

Methods: This prospective observational study was conducted over 12 months in the psychiatry outpatient department. Forty-five drug-naïve adult patients with newly diagnosed GAD (ICD-10 criteria) prescribed SSRI monotherapy were enrolled using systematic random sampling. ADRs were monitored using structured proformas and assessed using 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 45 GAD patients (mean age 36.0 ± 1.92 years; M:F = 0.95:1), 88 ADRs were reported. Escitalopram was most frequently implicated (53.3%), followed by paroxetine (28.9%). Central nervous system ADRs predominated (50%), with headache (11.4%), dizziness (10.2%), and drowsiness (9.1%) being most common. Gastrointestinal ADRs accounted for 33%. Most ADRs were mild (88.6%) and non-preventable (90.9%). All ADRs were classified as "possible" by

causality assessment. Tobacco use showed significant association with multiple ADR occurrence ($p=0.035$).

Conclusion: SSRIs demonstrate an acceptable safety profile in GAD management with predominantly mild, manageable ADRs. Enhanced pharmacovigilance, patient education regarding lifestyle modifications, and routine cognitive monitoring may optimize therapeutic outcomes in rural populations.

Keywords: Generalized anxiety disorder; Selective serotonin reuptake inhibitors; Adverse drug reactions; Pharmacovigilance; Montreal Cognitive Assessment; Rural India.

INTRODUCTION

Generalized anxiety disorder (GAD) represents one of the most prevalent psychiatric conditions globally, affecting approximately 6% of individuals at some point during their lifetime [1]. Characterized by persistent, excessive worry about multiple domains accompanied by physical symptoms including restlessness, muscle tension, fatigue, difficulty concentrating, irritability, and sleep disturbances, GAD substantially impairs quality of life, occupational functioning, and interpersonal relationships [2]. In India, the prevalence of anxiety disorders is estimated at 2.57%, though underdiagnosis remains common, particularly in rural areas where mental health literacy is limited [3].

The World Health Organization (WHO) recognizes anxiety disorders as major contributors to the global burden of disease, associated with significant disability, reduced productivity, increased healthcare utilization, and elevated suicide risk [1]. GAD frequently coexists with other psychiatric disorders, particularly depression, and medical comorbidities including cardiovascular disease and metabolic syndrome, complicating treatment and prognosis [2]. Beyond individual suffering, GAD imposes substantial societal costs through work absenteeism, reduced productivity, and increased healthcare expenditure.

Selective serotonin reuptake inhibitors (SSRIs) represent first-line pharmacological treatment for GAD based on robust evidence from randomized controlled trials demonstrating efficacy, tolerability, and favorable safety profiles compared to older anxiolytic agents such as benzodiazepines [4]. SSRIs selectively inhibit presynaptic serotonin reuptake, enhancing serotonergic neurotransmission implicated in anxiety regulation. Their relative lack of anticholinergic, antihistaminic, and alpha-adrenergic effects confers superior tolerability compared to tricyclic antidepressants [5]. Despite widespread clinical use, SSRIs are not devoid of adverse drug reactions (ADRs).

Adverse drug reactions are defined by the WHO as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease" [6]. Common SSRI-associated ADRs include gastrointestinal disturbances (nausea, diarrhea), sexual dysfunction, sleep alterations, weight changes, and neuropsychiatric manifestations (anxiety exacerbation, restlessness, headache) [7]. While pre-marketing clinical trials establish basic safety profiles, they often fail to detect uncommon ADRs, those occurring with prolonged therapy, or reactions in special populations, underscoring the importance of post-marketing pharmacovigilance [8].

The Pharmacovigilance Programme of India (PvPI), initiated in 2010 and coordinated by the Indian Pharmacopoeia Commission, 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, particularly in rural settings [10].

Recent pharmacovigilance studies have documented varying ADR patterns with SSRIs in psychiatric populations. Sisay et al. (2021) reported central nervous system and gastrointestinal manifestations as predominant ADR categories in patients with major depressive disorders [11]. Sankhi et al. (2020) observed that most SSRI-related ADRs were mild in severity and non-preventable [12]. However, data specifically characterizing ADR profiles in Indian patients with GAD remain scarce.

Furthermore, most existing studies focus on depression rather than anxiety disorders, leaving a significant knowledge gap.

Cognitive dysfunction in GAD has received increasing attention, with research demonstrating deficits in attention, inhibition, and executive function [13]. While SSRIs are hypothesized to exert pro-cognitive effects through serotonergic modulation and neuroplastic mechanisms, evidence regarding their impact on cognition in GAD patients remains limited and inconsistent. The Montreal Cognitive Assessment (MoCA) provides a validated brief screening instrument sensitive to detecting cognitive changes in psychiatric populations [14].

Rural Indian populations face unique challenges including limited mental health literacy, healthcare access barriers, cultural stigma surrounding psychiatric illness, high illiteracy rates, and distinct lifestyle habits such as tobacco and hookah use. The Mewat region of Haryana, where this study was conducted, exemplifies these characteristics with literacy rates of 51.7% overall and female literacy at 36.6%, limited healthcare infrastructure, and predominantly agricultural occupation [3]. Understanding ADR patterns in this context is essential for developing culturally appropriate patient education strategies and optimizing therapeutic protocols.

Research Gap: Despite the high prevalence of GAD and widespread SSRI use as first-line therapy, prospective data examining ADR profiles and sequential cognitive changes during SSRI treatment in Indian patients with GAD remain scarce. Most existing pharmacovigilance studies focus on Western populations or depressive disorders, limiting applicability to anxiety disorders in resource-limited settings.

Aim: The present study aimed to identify and characterize adverse drug reactions associated with SSRI use in patients with generalized anxiety disorder, evaluate their causality, severity, and preventability, and assess sequential cognitive function changes over six weeks 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 (SHKM GMC), Nuh, Haryana, India. SHKM GMC is a 600-bed tertiary care teaching hospital affiliated with Pt. B.D. Sharma University of Health Sciences, Rohtak, serving as the primary 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 from June 2023 to May 2024.

2.2 Study Population and Sampling

The target population comprised drug-naïve adult patients with newly diagnosed generalized anxiety disorder attending the psychiatry outpatient department. GAD diagnosis was established by qualified psychiatrists using International Classification of Diseases-10 (ICD-10) diagnostic criteria (F41.1 - Generalized Anxiety Disorder).

Inclusion Criteria:

- Age 18-60 years
- Newly diagnosed GAD per ICD-10 criteria
- Drug-naïve for all psychotropic medications
- Prescribed SSRI monotherapy by treating psychiatrist
- Willing and able to provide written informed consent

Exclusion Criteria:

- Comorbid psychiatric disorders (including depression, substance use disorders, psychosis)
- Significant medical comorbidities requiring polypharmacy
- Neurological disorders affecting cognition

Geriatric patients (>60 years)
Unwillingness to provide informed consent

2.3 Sample Size and Sampling Method

Based on an anxiety disorder prevalence of 2.57% in India, with 95% confidence level and 5% precision, the calculated sample size was 83 using the formula: $n = (Z^2 \times p \times (1-p)) / d^2$. Systematic random sampling was employed, screening every third eligible patient. From a total cohort of 96 patients (51 depression, 45 GAD), the 45 patients with GAD formed the study population.

2.4 Data Collection

Comprehensive sociodemographic 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, occupation, marital status, income level, lifestyle habits (smoking, alcohol, tobacco use), family psychiatric history, and prescribed SSRI details.

Suspected ADRs were identified through patient self-reporting, systematic inquiry using structured questionnaires, and review of medical records. Each ADR was documented using the PvPI ADR reporting form (Version 1.4) and reported to the National Coordinating Centre through Vigiflow software.

2.5 Assessment Tools

Causality Assessment: The WHO-Uppsala Monitoring Centre (WHO-UMC) 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 additional therapy), or severe (potentially life-threatening, causing permanent disability, or requiring hospitalization).

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 2019 and analyzed using IBM SPSS Statistics 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 $p < 0.05$.

2.7 Ethical Considerations

The study was conducted per the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants. Confidentiality and anonymity were maintained throughout. The study imposed no financial burden on participants and involved no experimental interventions.

3. Results

3.1 Demographic and Clinical Characteristics

A total of 45 patients with newly diagnosed GAD who were initiated on SSRI monotherapy completed the six-week follow-up.

Table 1: Demographic and Clinical Characteristics of GAD Patients (N=45)

Parameter	Category	Frequency (n)	Percentage (%)
Age Groups	18-29 years	15	33.3
	30-49 years	21	46.7
	50-60 years	9	20.0
	Mean $\pm$ SD	36.0 $\pm$ 1.92 years	Range: 18-60
Gender	Male	22	48.9
	Female	23	51.1
	M:F ratio	0.95:1	-
Educational Status	Illiterate	17	37.8
	Primary school	15	33.3
	Secondary school	6	13.3
	Higher secondary	6	13.3
	Graduate	1	2.2
Marital Status	Married	42	93.3
	Unmarried	3	6.7
BMI Category	Underweight (<18.5)	11	24.4
	Normal (18.5-24.9)	17	37.8
	Overweight (25-29.9)	12	26.7
	Obese ($\geq$ 30)	5	11.1
	Mean BMI $\pm$ SD	23.1 $\pm$ 4.5 kg/m ²	-
Tobacco Use	Yes	16	35.6
	No	29	64.4
Smoking	Yes	10	22.2
	No	35	77.8
Alcohol Use	Yes	0	0
	No	45	100
SSRI Prescribed	Escitalopram	24	53.3
	Paroxetine	13	28.9
	Sertraline	4	8.9
	Fluoxetine	4	8.9
ADR Pattern	Single ADR	11	24.4
	Multiple ADRs	34	75.6

The mean age was 36.0 $\pm$ 1.92 years, with the highest representation in the 30-49 years age group (46.7%). Gender distribution was nearly equal (M:F = 0.95:1). Educational profile revealed 37.8% illiteracy, reflecting rural demographic characteristics. The majority were married (93.3%). BMI analysis showed 62.2% fell outside normal weight ranges. Lifestyle assessment revealed 35.6% tobacco use, 22.2% smoking, and no alcohol consumption.

Escitalopram was the most frequently prescribed SSRI (53.3%), followed by paroxetine (28.9%), sertraline (8.9%), and fluoxetine (8.9%). The majority of patients (75.6%) experienced multiple ADRs.

3.2 Adverse Drug Reaction Profile

Table 2: System-Wise Distribution and Characteristics of ADRs in GAD Patients (N=45, Total ADRs=88)

ADR Category	Number of ADRs	Percentage	Specific ADRs (n)
Central Nervous System	44	50.0%	Headache (10), Dizziness (9), Drowsiness (8), Lethargy/fatigue (7), Restlessness (4), Anxiety (3), Confusion (2), Dystonia (1)
Gastrointestinal	29	33.0%	Nausea (8), Dry mouth (7), Bloating (6), Constipation (4), Diarrhea (3), Decreased appetite (1)
Cardiovascular	5	5.7%	Palpitations (3), Dizziness (2)
Miscellaneous	10	11.4%	Sleep disturbances (4), Weight changes (3), Others (3)
Causality (WHO-UMC)			
Possible	88	100%	-
Probable/Likely	0	0%	-
Severity (Hartwig)			
Mild	78	88.6%	No intervention required
Moderate	10	11.4%	Required symptomatic treatment
Severe	0	0%	-
Preventability			
Not Preventable	80	90.9%	-
Probably Preventable	8	9.1%	-
Definitely Preventable	0	0%	-

Among 45 GAD patients, 88 ADRs were reported. Central nervous system manifestations predominated (50%), with headache (11.4%), dizziness (10.2%), and drowsiness (9.1%) being most frequent. Gastrointestinal ADRs accounted for 33%, primarily nausea (9.1%) and dry mouth (8.0%). Cardiovascular ADRs were uncommon (5.7%).

All ADRs were classified as "possible" by WHO-UMC causality assessment. Severity analysis revealed 88.6% mild ADRs requiring no intervention and 11.4% moderate ADRs managed with symptomatic treatment (pantoprazole and domperidone for nausea). No severe ADRs occurred. Preventability assessment indicated 90.9% non-preventable ADRs, with 9.1% probably preventable, primarily related to suboptimal patient education.

3.3 Factors Associated with ADR Occurrence and Cognitive Function

Table 3: Demographic Factors Associated with Multiple ADR Occurrence in GAD Patients

Parameter	Single ADR n (%)	Multiple ADRs n (%)	χ^2	p-value
Age Group			2.200	0.333
18-29 years	5 (33.3)	10 (66.7)		
30-49 years	3 (14.3)	18 (85.7)		
≥50 years	3 (33.3)	6 (66.7)		
Gender			2.722	0.099
Male	3 (13.6)	19 (86.4)		
Female	8 (34.8)	15 (65.2)		
Tobacco Use			4.450	0.035*
Yes	1 (6.3)	15 (93.8)		
No	10 (34.5)	19 (65.5)		
Educational Status			0.825	0.935
Illiterate	4 (23.5)	13 (76.5)		

Primary school	4 (26.7)	11 (73.3)		
Secondary+	3 (23.1)	10 (76.9)		
SSRI Type			3.576	0.311
Escitalopram	7 (29.2)	17 (70.8)		
Paroxetine	2 (15.4)	11 (84.6)		
Sertraline	2 (50.0)	2 (50.0)		
Fluoxetine	0 (0)	4 (100)		

*Statistically significant at $\alpha = 0.05$ level

Tobacco use showed statistically significant association with multiple ADR occurrence ($p=0.035$), with tobacco users experiencing higher ADR frequency. Age, gender, educational status, and SSRI type did not demonstrate significant associations with ADR patterns.

4. Discussion

This prospective observational study provides comprehensive insights into the ADR profile of SSRIs in patients with GAD in a rural Indian tertiary care setting. The findings underscore the generally favorable safety profile of SSRIs while highlighting specific patterns requiring clinical attention and opportunities for enhanced pharmacovigilance.

The mean age of 36 years with predominant representation in the 30-49 years group (46.7%) aligns with epidemiological data identifying this demographic as peak-risk for anxiety disorders due to occupational stress, family responsibilities, and socioeconomic pressures [2]. The nearly equal gender distribution (M:F = 0.95:1) in our GAD cohort differs from some Western studies reporting female preponderance in anxiety disorders, possibly reflecting cultural barriers limiting healthcare-seeking among women in rural settings or referral patterns to tertiary care.

Escitalopram emerged as the most frequently prescribed SSRI (53.3%), accounting for a substantial proportion of ADRs. This pattern mirrors findings from other Indian studies where escitalopram dominated SSRI prescriptions for anxiety disorders due to perceived superior efficacy, favorable tolerability, and availability in public healthcare formularies [4,5]. The high ADR frequency with escitalopram likely reflects prescription prevalence rather than inherently greater toxicity. Paroxetine, prescribed in 28.9% of patients, showed comparable ADR rates, consistent with literature documenting its efficacy but also higher discontinuation rates due to adverse effects.

The predominance of central nervous system ADRs (50%) corresponds with serotonergic mechanisms of SSRIs and their effects on neuronal circuits regulating arousal, anxiety, and pain perception. Headache (11.4%), the most frequent CNS manifestation, typically represents a transient early adverse effect that often resolves with continued therapy. Dizziness (10.2%) and drowsiness (9.1%) similarly reflect enhanced serotonergic tone in vestibular pathways and sleep-wake regulatory centers [7]. These findings align with pharmacovigilance studies in anxiety populations reporting CNS symptoms as predominant SSRI-related ADRs [11,12].

Interestingly, only 3.4% of patients reported SSRI-induced anxiety exacerbation, contrasting with findings by Naslund et al. (2017) who observed high incidence of early SSRI-induced anxiety in depression trials [15]. This discrepancy may be attributed to the routine co-prescription of clonazepam for the first 2-3 weeks of SSRI therapy in our setting, potentially mitigating early anxiety symptoms. This practice, while not universally recommended, appears beneficial in GAD patients initiating SSRI therapy.

Gastrointestinal ADRs (33%) align with the high concentration of serotonin receptors in the enteric nervous system. Activation of 5-HT₃ receptors in the chemoreceptor trigger zone and gastrointestinal tract mediates nausea (9.1%), while anticholinergic properties of some SSRIs contribute to dry mouth (8.0%) [7]. The relatively low frequency of diarrhea compared to Western populations may reflect dietary differences, gut microbiome variations, or genetic polymorphisms affecting serotonin transporter expression in Indian populations.

Notably absent from our findings were reports of sexual dysfunction, a commonly cited SSRI adverse

effect. This discrepancy likely reflects cultural reticence in discussing sexual concerns in the conservative rural Mewat population rather than true absence. Future studies incorporating validated sexual function questionnaires administered by same-gender clinicians may better capture this important ADR domain [11].

The causality assessment classified all ADRs as "possible" rather than "probable," reflecting inherent challenges in psychiatric pharmacovigilance. GAD itself manifests with somatic symptoms (restlessness, muscle tension, fatigue, sleep disturbance) that overlap with SSRI adverse effects, complicating attribution. Additionally, dechallenge and rechallenge are clinically inappropriate in chronic anxiety management, limiting the ability to achieve higher causality categories [6].

Severity assessment revealed predominantly mild ADRs (88.6%) requiring no intervention, with 11.4% moderate cases managed symptomatically. The absence of severe ADRs reinforces the favorable benefit-risk profile of SSRIs in uncomplicated GAD without medical comorbidities. This severity distribution aligns with findings from Sankhi et al., who reported 89% mild ADRs in their antidepressant cohort [12]. The mild nature of most ADRs supports SSRI continuation with reassurance and patient education rather than discontinuation.

Preventability analysis indicated 90.9% non-preventable ADRs, reflecting appropriate prescribing practices, dosing, and monitoring. The 9.1% probably preventable ADRs primarily involved inadequate patient counselling regarding expected adverse effects, issues potentially addressable through enhanced patient education programs adapted to low-literacy populations.

The significant association between tobacco use and ADR occurrence ($p=0.035$) merits attention. Tobacco smoke contains polycyclic aromatic hydrocarbons that induce hepatic cytochrome P450 enzymes, potentially accelerating SSRI metabolism and creating fluctuating drug levels predisposing to adverse effects. This finding emphasizes the importance of tobacco cessation counselling as an integral component of GAD management. The high prevalence of tobacco and hookah use in Mewat underscores region-specific challenges requiring culturally tailored interventions.

As SSRIs alleviate anxiety symptoms, cognitive resources are freed for normal processing. Additionally, serotonergic enhancement promotes neuroplasticity, stimulates hippocampal neurogenesis, and modulates cholinergic, dopaminergic, and glutamatergic pathways implicated in cognition [13] [14].

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. Self-reported ADRs without systematic laboratory monitoring may underestimate subclinical effects. The absence of sexual dysfunction likely reflects cultural underreporting. Exclusion of elderly patients and those with comorbidities restricts generalizability. The small sample size ($n=45$) limits power for subgroup analyses.

Clinical Implications: These findings support SSRI use as first-line pharmacotherapy for GAD in rural Indian settings, with predominant mild, manageable ADRs. Proactive patient education regarding common ADRs may improve adherence. Tobacco cessation counseling should be integrated into GAD care pathways.

5. Conclusion

This prospective observational study demonstrates that SSRI therapy exhibits an acceptable safety profile in generalized anxiety disorder 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 known pharmacological actions of SSRIs. Escitalopram, as the most frequently prescribed agent, accounts for the highest absolute number of ADRs, though this 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 GAD care. The absence of severe ADRs reinforces SSRIs as

first-line therapy in resource-limited settings.

These findings contribute valuable real-world evidence to the limited pharmacovigilance data from rural Indian populations with anxiety disorders and underscore the necessity of ongoing post-marketing surveillance, enhanced patient education, culturally adapted counselling strategies to ensure patient safety and optimize therapeutic outcomes in diverse clinical contexts.

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