

ASSESSMENT OF ADVERSE DRUG REACTIONS OF ANTIDEPRESSANT DRUGS USED IN PSYCHIATRY DEPARTMENT OF A TERTIARY CARE HOSPITAL**VIRENDRA KUSHWAHA¹, POOJA AGRAWAL¹, SARITA SINGH^{1*}, DHANANJAY CHAUDHARY², AMIT K. VERMA¹, HIMANSHU SHARMA¹**¹Department of Pharmacology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India. ²Department of Psychiatry, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India. Email: saritasingh0512@gmail.com*Received: 31 January 2022, Revised and Accepted: 05 March 2022***ABSTRACT****Objective:** The aim of the study was to analyze adverse drug reactions (ADRs) reported in patients prescribed antidepressants at tertiary care hospital.**Methods:** A prospective and observational study was conducted during January 2020–July 2021 at Department of Pharmacology in collaboration with the Department of Psychiatry, GSVM Medical College, and Kanpur. All patients diagnosed with depression and receiving pharmacotherapy were included in the study. ADRs were monitored using the standard form of the Central Drugs Standard Control Organization and causality was determined using the Naranjo algorithm. Data were evaluated for patient's demography, risk factors for ADRs, and pattern of ADR.**Results:** A total of 293 ADRs were recorded from 110 patients. The most common ADRs observed were anxiety (47.42%) and insomnia (19.22%). Men (58.18%) were most commonly affected than women (41.82%). The most common causal drugs among antidepressants were Escitalopram (27.27%) and Venlafaxine (21.81%), respectively. The most common system involved was central nervous system (53.24%) followed by gastrointestinal system (41.63%). The majority of ADRs (97.95%) were possible according to the Naranjo's scale.**Conclusion:** Anxiety, insomnia, and dizziness were the common ADRs which were associated with the use of antidepressants. This study offers a representative profile of the ADRs which can be expected in the psychiatry outpatients.**Keywords:** Depression, Antidepressants, Non-compliance, Naranjo's Scale.© 2022 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2022v15i4.44287>. Journal homepage: <https://innovareacademics.in/journals/index.php/ajpcr>**INTRODUCTION**

Depression is characterized by persistent sadness, accompanied by an inability to carry out daily activities, feelings of worthlessness, guilt or hopelessness, and thoughts of self-harm [1]. Depression is a common psychiatric disorder affecting more than 264 million people around the globe. It is a leading cause of worldwide disability and a major contributor to the overall global burden of disease [2]. It is treatable with psychotherapy, also known as counseling, antidepressant medication, or a combination of these [3,4].

Antidepressant drugs are the most effective and widely used forms of the treatment for depression but this does not mean they are free of adverse drug reactions (ADR) [2]. Along with the therapeutic effect, almost every drug has side effects or adverse effects [5].

An ADR, as per the WHO, is defined as "a response to a drug which is noxious unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or for modification of physiological function." These reactions pose a significant problem in view of increased morbidity and mortality, increasing costs of health care and poor compliance [6]. Large number of ADRs associated with use of psychiatric medication due to their effect on multiple dopaminergic pathways [7]. Common psychiatric disorders are anxiety disorders including panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, bipolar disorder, depression, mood disorder, and psychotic disorder like Schizophrenia [8].

ADR monitoring is a process of continuously monitoring undesirable effects suspected to be associated with use of medical products. According to the Centre for Health Policy Research, more than 50% of the approved drugs were associated with some type of adverse

reaction not detected before approval [9]. Pharmacovigilance (PV) is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects or any other drug-related problem [10]. The association of antidepressant drugs with ADR is common and can occur even at the normal doses used in the management of acute and maintenance phases of psychiatric disorder [11].

Depressive disorders represent a wide-spread mental disorder with a lifetime prevalence [12]. Commonly used group of antidepressant drugs is selective serotonin reuptake inhibitors (SSRIs), serotonin, and norepinephrine reuptake inhibitors, atypical antidepressants, tricyclic antidepressants, and monoamine oxidase inhibitors [13]. Newer antidepressant such as desvenlafaxine, levomilnacipran, vilazodone, and vortioxetine is included in our study. Almost all the psychiatric diseases have temporary cure and the treatment is lifelong [14].

ADR monitoring in the hospital setting is vital because it helps to understand the nature and type of ADRs and to identify high-risk patients for developing ADRs [15]. PV in India is still in infancy and ADR reporting rates are below 1% and require more data [16]. This might be due to lack of ADR reporting due to guilt, lack of awareness, motivation, ignorance, training, and time limitations among health-care personnel [17]. Thus, there are not many studies regarding ADRs of antidepressant drugs.

Now a days, mental health problem is very common due to change in life style. There is a lack of communication among people thus they are not able to deal with their emotions. Depression prevails in patient life makes them to seek help by the psychiatrist. Since depression requires long-term antidepressant treatment. Hence, this study is undertaken

to analyze the clinical spectrum of ADRs and assess the causality of the ADRs reported of different antidepressant drugs including newer antidepressant in Psychiatric Department, G.S.V.M Medical College, Kanpur.

MATERIALS AND METHODS

Materials

A prospective and observational study was conducted during January 2020–July 2021 at Department of Pharmacology in collaboration with the Department of Psychiatry, GSVM Medical College, Kanpur. Patients diagnosed with depression and are on antidepressants attending out Patient department of psychiatry were enrolled in the study. About 110 patients were enrolled in the study.

Inclusion criteria

The following criteria were included in the study:
Patients of both genders.

- Patients diagnosed with depression attending outpatient department of Psychiatry
- Patients who gave written informed consent

Exclusion criteria

The following criteria were excluded from the study:

- Patients unable to respond to verbal questions
- Pregnant/lactating females
- Patients with concomitant disorders such as diabetes mellitus, hypertension, and cardiovascular diseases.

Methods

This was a prospective and observational study. After receiving ethical clearance, all the patients who were on antidepressants were assessed for their demographic factors such as age, gender, literacy, and employment. In this study, the patient with depression will be acknowledged with the help of DASS -21 scale. Any adverse effects which were observed were recorded in the "Adverse Drug Event Reporting Form" which was prepared by the CDSCO, Government of India. The causalities of the event were assessed by the Naranjo's Scale. The data were compiled and converted into tables and graphs. The data were analyzed using Chi-square test and $p < 0.05$ was considered as statistically significant.

RESULTS

The present study was conducted in Department of Pharmacology in collaboration with Department of Psychiatry, G.S.V.M Medical College, Kanpur. A total number of 110 patients encountered with various types of ADRs during our study period, that is, January 2020–July 2021. A total number of ADRs recorded were 293. Hence, the burden of ADR due to antidepressant drug was 2.6 ADR per patient.

From table, it can be concluded that incidence of ADRs was more in male patients as compared to female counterpart. ADRs were more common in 21–40 year age group, Illiterate patients were found to be the risk factor for developing ADRs. In our study, employed population encountered ADRs more frequently than the unemployed ones.

Patient's distribution according to the treatment

Out of 110 patients who encountered ADRs, maximum patients were on Escitalopram followed by Venlafaxine, Desvenlafaxine, and so on.

Pattern of organ system-wise ADR burden

Maximum burden of ADRs was due to involvement of the central nervous system (CNS) followed by gastrointestinal, reproductive system, miscellaneous, and cardiovascular system.

Distribution of CNS-related ADRs

In our study among CNS ADRs, anxiety was found the most common ADR followed by insomnia, dizziness, headache, somnolence, and drowsiness.

Distribution of gastrointestinal system-related ADRs

In our study among gastrointestinal ADRs, constipation was found the most common ADR followed by dry mouth, nausea, vomiting, epigastric pain, etc.

Distribution of reproductive system-related ADRs

In our study among reproductive system, ADRs were very rare, where decreased libido was found the most common followed by diminished erection, painful ejaculation, decreased vaginal lubrication, etc.

Distribution of cardiovascular system ADRs

In our study, all cardiovascular ADRs were postural hypotension.

Distribution of miscellaneous ADRs

In our study, all miscellaneous ADRs were weight loss.

Analysis of various risk factors for development of various ADRs pertaining to antidepressants

CNS

We analyzed the various demographic parameters as a risk factor for developing CNS ADRs using appropriate statistical tests. The detail of analysis is shown in table

From table, it can be concluded that there was no significant difference in two population subgroups with respect to gender and employment. However, a significant difference ($p < 0.05$) was observed in literacy

Gastrointestinal ADRs

Analysis of various demographic parameters was also done as a risk factor for the development of gastrointestinal system-related ADRs. The details of statistical analysis are shown in table. From table, it can be concluded that there was no significant difference in two population subgroups with respect to gender and employment. However, a significant difference was observed in literacy.

Reproductive system ADRs

Analysis of various demographic parameters was also done as a risk factor for the development of gastrointestinal system-related ADRs. The detail of statistical analysis is shown in table. From table, it can be concluded that there was no significant difference in two population subgroups with respect to gender, employment, and literacy.

Distribution of ADRs according to the ADR types

All reported ADRs were categorized into six types according to the expanded Rawlins and Thompson classification. All the ADRs were of Type A. There were no ADR of Type – B, C, D, E, and F in our study.

Causality assessment of ADRs

All the ADRs were analyzed for the causality according to the Naranjo's probability scale. Out of total 293 ADRs, majority were in possible category (97.95%) followed by probable category (2.05%). There was no ADR which was classified as doubtful or definite category.

DISCUSSION

Our study evaluated ADRs due to antidepressants among depressive patients in the Department of pharmacology in collaboration with Department of Psychiatry in GSVM Medical College, Kanpur. ADRs are an important concern in the provision of antidepressant drugs. Mental and behavioral disorders are common mental health problems that directly affect work capacity and productivity in the person. Some people resist taking antidepressants because they do not like to admit that something is wrong with them. Others dislike the idea of being dependent on a chemical substance to keep their mood level or lacking a sense of control over life [1].

In our study, burden of ADR was 2.6/patient which was greater than the study done by Lucca et al. [18] (1.2 ADR/patient) and less than the study conducted by Sankhi et al. [19] (4.5 ADR/patient). This difference in per

patient burden of ADRs can be due to difference in drug treatment. The drug responsible in our study Escitalopram (SSRIs) and in study done by Sridhar *et al.* [20] was Fluoxetine. As per literature, SSRI causes more ADR than other antidepressants as SSRI are more commonly used.

In our study, maximum burden of ADR was found in males than female. Males (58.18%) affected more with ADR than female (41.8%) with male: female ratio 1.39. This is in line with the previous study Barvaliya *et al.* [8] (male (57.3%) was affected more with ADRs than female (42.7%) with male: female ratio 1.34). In other studies conducted by Lucca *et al.* [18], Sridhar *et al.* [20], and Sengupta *et al.* [10], observed male predominance with male: female ratio 1.05, 1.02, and 2.19, respectively, and differ with Sankhi *et al.* [19], the male-to-female ratio was 1:1.35, also females experienced a higher incidence of ADRs (5.56%) than males (3.63%). The gender difference in ADR frequency can be due to literacy rate more in males, they have more knowledge related to disease as compared to females. Females have less knowledge toward their disease, medication, and complication.

In our study, maximum patients who encountered ADRs were in age group 21-40 years. Mean age group of patients in our study was 32.5 years which is in consistent with study conducted by Barvaliya *et al.* [8], Sengupta *et al.* [10], Lucca *et al.* [18], Sridhar *et al.* [20], and Patel *et al.* [21], mean age of patients in these studies was 37.88 years, 34.4 years, 35.6 years, 39.31 years, and 36.15 years, respectively. This finding may be because of high prevalence of psychiatric illness in this age group (20-40), it can be due to the fact that this age group falls in reproductive age and hormonal changes are maximum. Differ with study conducted by Rajesh *et al.* [22] in which most common age group involved was 41-60 years. In our study, patients who were employed present with more ADRs than the unemployed ones. One plausible reason behind this finding can be that employed patients were economically sound and had better access to the treatment.

In our study, frequency of ADRs, there was no significant difference in two population subgroups with respect to gender, employment, and literacy, which differ from other study conducted by Sridhar *et al.* [20], Sengupta *et al.* [10] in which statistically significant finding was found between gender, employment, and age group.

In our study, literate patients were found to have more burden of ADR than the illiterate patients. This finding is similar with the previous study Sankhi *et al.* [19]; while differ with studies conducted by Bhuvana *et al.* [23] and Modayil *et al.* [24]. The most common drug responsible for ADR was Escitalopram of class SSRI in our study. This finding is in consistent with most of the previous studies (Sankhi *et al.* [19], Lucca *et al.* [18], Sridhar *et al.* [20], and Sengupta *et al.* [10] and differs from studies conducted by Barvaliya *et al.* [8] and Sankhi *et al.* [19] in which tricyclic antidepressants were most commonly implicated for the development of maximum burden of ADRs.

The most common organ system involved due to ADRs was CNS in our study. This finding is in line with some previous studies (Sridhar *et al.* [20], Sengupta *et al.* [10], and Barvaliya *et al.* [8]) and differs from other studies conducted by Sankhi *et al.* [19], Aburamadan *et al.* [25], and Driessen *et al.* [16] in which gastrointestinal system was most commonly involved.

In our study, employed patients were more commonly affected due to high stress level in their busy life. In our study, CNS ADRs in males are significant. Male patients were more engaged in their work, take more tension out of it, and have less time for themselves. In our study, Escitalopram was more commonly responsible for CNS adverse effects followed by Paroxetine and Amitriptyline. Among the antidepressants, SSRIs were found to be primarily associated with more ADRs than other antidepressants, due to overstimulation of 5-HT₂ receptors in the brain results in insomnia, anxiety, irritation, and worsening of symptoms of depression.

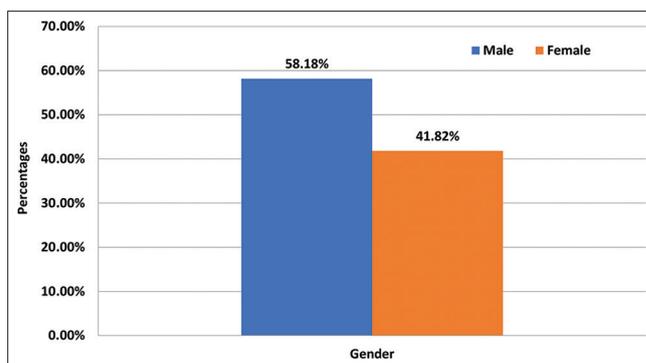


Fig. 1: Gender of the population

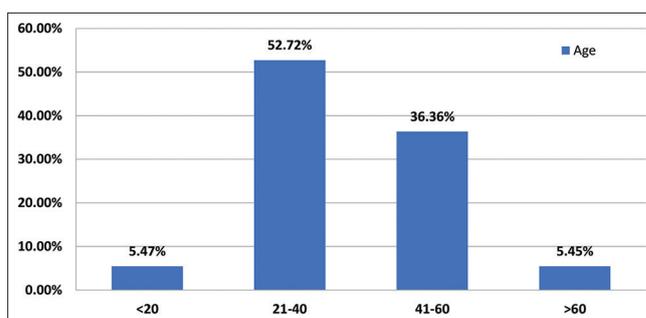


Fig. 2: Age group of the study population

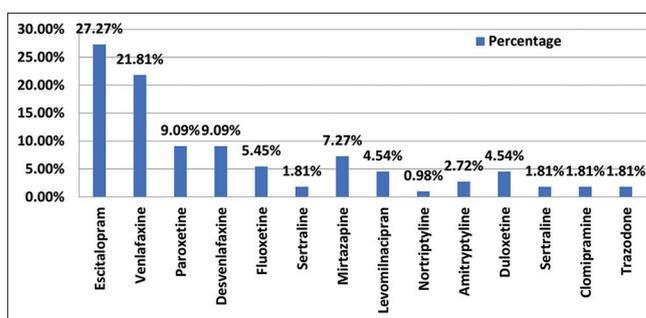


Fig. 3: Percentage of the patients according to the treatment

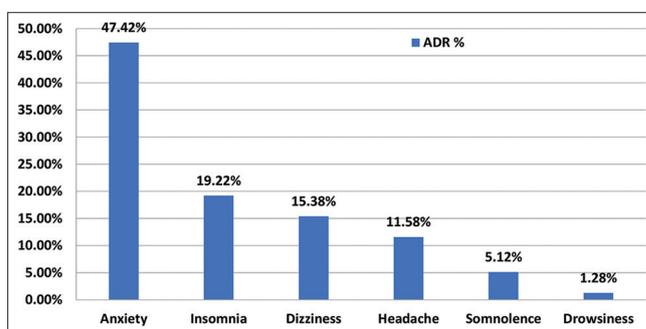


Fig. 4: Percentage of the central nervous system-related adverse drug reactions

In our study, gastrointestinal system ADRs were 41.63%. This finding is in line with studies conducted by Lucca *et al.* [18] (37.5%) and Grohmann *et al.* [26] (39.2%) and differs from the study conducted by Swathi *et al.* [27] (27.4%) [12]. wherein cardiovascular system was the predominant system affected by the ADR. ADRs such as constipation, gastritis, sedation, weight gain, oral ulcer, restlessness, erectile dysfunction, and tremor were more

common in patients taking SSRIs followed by TCAs. This might be explained on the basis of the mechanism of action of SSRIs, where stimulation of 5-HT3 receptors in the central and peripheral nervous systems causes gastrointestinal reactions such as gastritis, oral ulcers, and diarrhea.

Among gastrointestinal ADRs constipation was most commonly seen in our study which is in line with studies done by Nagpal et al. [28] and Lucca et al. [18] and differs with the study done by Reddy et al. [29] in which gastritis was the most common gastrointestinal ADR followed by dry mouth.

In our study, decreased libido was the common among the reproductive system ADRs which in line with studies done by Nagpal et al. [28] and Reddy et al. [29] (3.2%). The most of the ADRs were of Type A in our study. This finding is in line with studies conducted by Sridhar et al. [20] (95%) and Sengupta et al. [10] (93%).

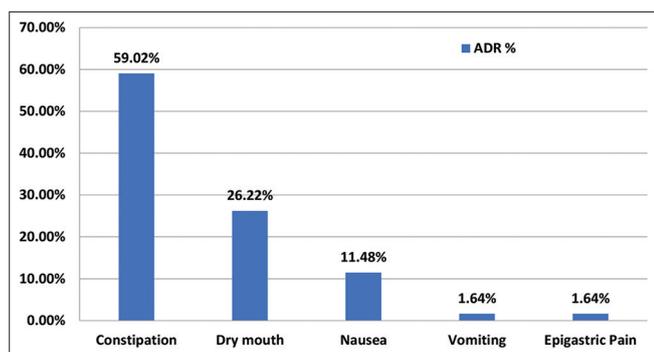


Fig. 5: Percentage of gastrointestinal tract-related adverse drug reactions

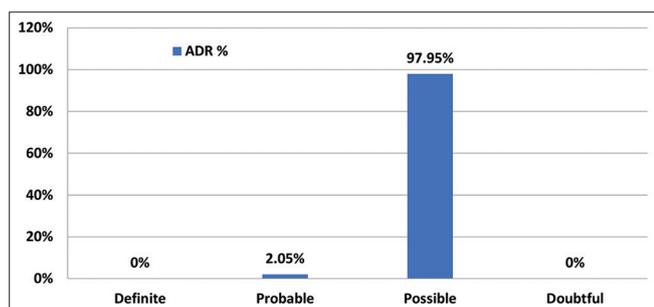


Fig. 6: Percentage of causality assessment of adverse drug reactions

Table 1: Demographic profile of patients

S. No.	Characteristics	n=110, n (%)
1	Gender	
	Male	64 (58.18)
	Female	46 (41.82)
2	Age (years)	
	<20	6 (5.47)
	21-40	58 (52.72)
	41-60	40 (36.36)
	>60	6 (5.45)
3	Literacy	
	Literate	71 (64.55)
	Illiterate	39 (35.45)
4	Employment	
	Employed	62 (56.36)
	Unemployed	48 (43.64)

n: Number of patients

On causality scale, the most of the ADRs in our study were of possible type. This finding is in line with most of the previous studies (Reddy et al. [29], Patel et al. [21], Bhuvana et al. [23], Nagpal et al. [28], and Barvaliya et al. [8]) and differs from some studies (Sankhi et al. [19], Aburamadan et al. [25], and Gummadi et al. [30]) in which most of ADRs were of probable type.

Table 2: Organ system-wise adverse drug reaction burden

Serial number	Organ system	Number of ADRs (%)
1	Central nervous system	156 (53.24)
2	Gastrointestinal	122 (41.63)
3	Reproductive system	6 (2.04)
4	Miscellaneous	6 (2.04)
5	Cardiovascular system	3 (1.05)
	Total	293 (100)

ADRs: Adverse drug reactions

Table 3: Reproductive system-related adverse drug reactions

Serial number	ADR	No	ADR (%)
1	Decreased libido	3	50
2	Painful ejaculation	2	33.34
3	Diminished erection	1	16.66
4	Decreased vaginal lubrication	0	0
	Total	6	100

ADR: Adverse drug reaction

Table 4: Central nervous system ADRs

S. No.	Characteristics	CNS ADRs		χ ²	p
		Yes (n=75)	No (n=35)		
1	Gender			1.347	0.2465
	Male	45	25		
	Female	30	10		
2	Age			4.325	0.2285
	<20	4	4		
	21-40	29	15		
	41-60	22	10		
	>60	20	6		
3	Employment			1.443	0.2302
	Employed	47	26		
	Unemployed	28	9		
4	Literacy			3.553	0.05946*
	Literate	49	29		
	Illiterate	26	6		

*p<0.05 (significant). CNS: Central nervous system, ADRs: Adverse drug reactions

Table 5: Gastrointestinal adverse drug reactions

S. No.	Characteristics	GIT system ADRs		χ ²	p
		Yes (n=49)	No (n=61)		
1	Gender			1.61	0.2048
	Male	28	42		
	Female	21	19		
2	Age			0.5695	0.9034
	<20	6	5		
	21-40	24	32		
	41-60	12	16		
	>60	7	8		
3	Employment			1.542	0.2147
	Employed	28	29		
	Unemployed	19	32		
4	Literacy			5.84	0.01567*
	Literate	20	39		
	Illiterate	29	22		

*p<0.05 (significant). GIT: Gastrointestinal tract, ADRs: Adverse drug reactions

Table 6: Reproductive system adverse drug reactions

S. No.	Characteristics	Reproductive system ADRs		χ^2	p
		Yes (n=6)	No (n=104)		
1	Gender			1.335	0.2486
	Male	4	88		
	Female	2	16		
2	Age			0.8971	0.3436
	<20	0	7		
	21-40	5	60		
	41-60	1	35		
	>60	0	2		
3	Employment			0.2348	0.628
	Employed	4	60		
	Unemployed	2	46		
4	Literacy			0.2348	0.628
	Literate	4	60		
	Illiterate	2	46		

ADRs: Adverse drug reactions

Table 7: Representing adverse drug reaction type percentage

S. No.	ADR type	Number of ADRs (%)
1	A	293 (100)
2	B	0
3	C	0
4	D	0
5	E	0
6	F	0
	Total	293 (100)

ADRs: Adverse drug reactions

CONCLUSION

- There is a need for the development of a uniform, prospective, and well-defined monitoring program to enhance awareness and promote research into the costly and dangerous phenomenon of ADRs in depressed medically ill patients for drugs and patients in general
- SSRIs being the most common class of drugs implicated for the ADRs. This prospective surveillance study provides a representative data of ADR profile of the antidepressants likely to be encountered in Indian psychiatric patients. Constant vigil in early detection and reporting of ADRs and subsequent management can make the therapy with antidepressants safer and effective
- ADRs go hand in hand with drugs in the treatment of psychiatric illnesses due to chronicity of the disease and long duration of the treatment process
- Identifying risk factors such as age, gender, educational status, and earning status for occurring of ADRs are of crucial importance to optimize the initial dose of antidepressant drugs before initiating therapy and to prevent severity caused by antidepressants
- In our study, the most common ADRs associated with currently used antidepressant drugs are anxiety (47.42%), constipation (59.02%), dry mouth (26.22%), insomnia (19.22%), and headache (11.58%)
- CNS ADRs are common with SSRI while gastrointestinal system ADRs are more common with tricyclic antidepressants. Hence, these drugs should be prescribed cautiously with the direction that patients receiving these regimens should be monitored for CNS and gastrointestinal system ADRs, respectively.

AUTHORS' CONTRIBUTIONS

Dr. Virendra Kushwaha, Dr. Pooja Agrawal, Dr Sarita Singh, and Dr. Dhananjay Choudhary contributed substantially to the conception, design of the study, analysis, and interpretation of data. All authors discussed the results and commented on the manuscript.

CONFLICT OF INTEREST STATEMENT

None to declare.

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