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Research Article

ASSESSMENT OF CASUALITY AND SEVERITY OF VARIOUS REPORTED ADVERSE DRUG REACTIONS BY DIFFERENT CLASSES OF ANTI DEPRESSANT DRUGS

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ABSTRACT

Depression being a most common mental disorder is estimated to effect 350 million people. The demand for curbing depression and other mental health conditions are on the rise globally. The mean age of the study population was 38.4 years and 66.8% of them were females and 33.2% of them were males. Major depressive disorder (60.9%) and generalised anxiety disorder (21.8%) were the most common diagnoses. In our study SSRIs were more preffered drugs than other antidepressants. Among SSRIs, escitalopram are commonly used drugs followed by mirtazipine and sertraline respectively. A total of 1194 ADRs with 33 different types were observed in 207 patients, with an overall prevalence of about 94.1. All the reported ADRs were mild to moderate in severity according to modified Hart wig and Siegel scale. The most common reported ADRs were dry mouth (54.1%), nausea (49.1%), sedation (42.1%) and increased apeptite (39.4%). The most common organ system involved was gastrointestinal. Most of the ADRs were found to be associated with the use of escitalopram followed by mirtazipine and sertraline.

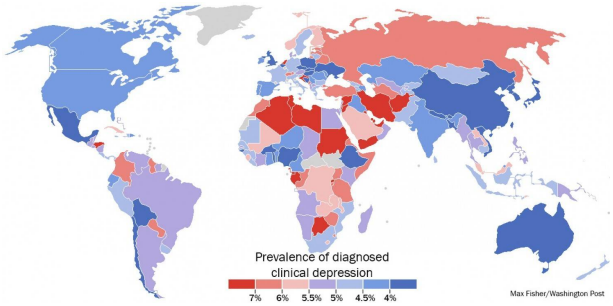
INTRODUCTION

Depression is the most common psychiatric illness of older people and is often undiagnosed. It is not only the leading cause of suicide in older people but has a negative impact on quality of life and increases disability from other physical illness. It is also an independent predictor of mortality. Although effective treatment exists, depression is under-recognized and often undertreated.

Today, depression is estimated to affect 350 million people. At its worst, depression can lead to suicide. Almost one million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day. For every person who completes a suicide, 20 or more may attempt to end his or her life. The facts and figures around Mental Health are alarming.

Antidepressants

Antidepressants can reduce the symptoms of depression but their effect may also be unsatisfactory or lead to serious deterioration in the patient's condition. Antidepressants are among the world's most frequently prescribed drugs. Current antidepressant drugs are effective and generally well tolerated but non-compliance remains worrisome. Up to 70% of patients taking antidepressants are noncompliant as a result of either missed doses or premature discontinuation.



Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality. Adverse drug events can range from mild to life threatening reactions resulting in inconvenience or serious morbidity and mortality besides being a financial burden on the society. Recent works of adverse drug reaction monitoring in hospitalized patients have suggested that adverse drug reactions are a major public health concern. Adverse drug reactions are responsible for 5-7% of hospital admissions occur in 10-20% hospital inpatients, causing death in 0.1% of medical and 0.01 % of surgical inpatients.

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Aims and Objectives

To study the occurrence of various adverse drug reactions caused by anti depressant drugs.

- To correlate the adverse drug reactions caused by antidepressant drugs with age and sex of the patients.
- To assess severity and causality of the reported adverse drug reactions.

After getting approval from the Institutional Ethical Committee, the prospective observational study was conducted by the Department of Medicine in collaboration with the psychiatric Out-Patient Department of Institute of Mental Health and Neurosciences, Department of Psychiatry (SMHS Hospital), Government Medical College, Srinagar.

Inclusion Criteria

1. All the patients of any age and either gender of psychiatric disorders attending psychiatric outpatient department who were prescribed different antidepressant drugs were included.
2. The baseline and other relevant investigations of the included patients were recorded at the start of the study and these investigations were repeated wherever required.

Exclusion Criteria

1. Patient with severe psychiatric or medical illness such as acute psychosis, cardiac and hepatic failure.
2. Patients who are unable to cooperate.
3. Patients with inability to give consent.

Patients or their attendants were interviewed as per the prescribed format after taking their consent. Information was obtained about patient demographics (age, sex, residence, occupation), personal characteristics (smoking status), clinical characteristics (duration, type and severity of illness) and the drug history if any. Patients were followed up on weekly basis upto a minimum of 12 weeks and for the development of any adverse drug reaction. An assessment of causality and allocation of adverse drug reactions to these different categories was done using WHO-UMC scale.

WHO-UMC Scale

The WHO-UMC system has been developed in consultation with National Centers participating in the programme for international Drug Monitoring and is meant as a practical tool for assessment of case programme for international Drug Monitoring and is meant as a practical tool for assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. This method gives guidance to the general arguments which should be used to select one category over another.

Severity of Adverse Drug Reactions

The severity of adverse drug reactions was determined by using modified Hart wig and Siegel scale (1992) as given below:-

Mild: Adverse drug reactions which were self limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay

Moderate: Adverse drug reactions were defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in < 24 hrs or change in drug therapy or specific treatment to prevent a further outcome.

Severe: Adverse drug reactions were those that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization or required intensive medical care.

Lethal: Adverse drug reactions were those that directly or indirectly contributed to patient's death.

Patient outcomes will be reported as

- Fatal
- Fully recovered (Patient fully recovered during hospitalization)
- Recovering (patient recovering, but not fully recovered during hospitalization)
- Unknown (not documented after initial report in chart)

Term	Description
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacolo-gically, pathologically) • Event definitive pharmacologically or phenomeno-logical (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). • Rechallenge satisfactory, if necessary
Probable/ likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal maybe lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable(but not impossible) • Disease or other drugs provide plausible explanation.
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessible/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is in sufficient or contradictory • Data cannot be supplemented or verified.

Statistical Methods

Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Continuous variables were summarized as Mean±SD. Categorical variables were summarized as percentages. Chi-square test was used to test for independence of two categorical variables. An exact p-value (two-sided) was reported when chi-square was not valid (as per Cochran criteria). Bar charts and pie charts were used for graphical presentation of data. P-value less than 0.05 was considered statistically significant. All P-values were two tailed.

RESULTS AND OBSERVATIONS

Table 1 Distribution of study population as per gender

Gender	No.	%age
Male	73	33.2
Female	147	66.8
Total	220	100

Table 1 reveals the distribution of study population according to the gender. The study population comprised of 66.8% females and 33.2% males.

Table 2 Distribution of study population according to occupation

Occupation	No.	%age
Housewife	99	45.0
Government Employee	43	19.5
Student	40	18.2
Labour	19	8.6
Business man	17	7.7
Skilled Worker	2	0.9
Total	220	100

Table 2 reveals the distribution of study population according to occupation. Housewives 45.0% and Government employees 19.5% comprised the two common groups in the study population followed by the student 18.2%.

Table 3 Distribution of study population according to diagnosis

Diagnosis	No.	%age
Major Depressive Disorder	134	60.9
Generalized Anxiety Disorder	48	21.8
Obsessive Compulsive Disorder	28	12.7
Somatoform Disorder	10	4.5
Total	220	100

Table 3 indicates the distribution of study population according to the diagnosis. Major depressive disorder was the most common diagnosis in the study population. Out of total 220 patients, 134 (60.9%) were diagnosed as major depressive disorder by psychiatrist.

Table 4 Distribution of antidepressant drugs as per class in studied population

Class of Drug	Name of Drug	No.	%age
SSRI	Escitalopram	91	41.4
	Sertraline	21	9.5
	Paroxetine	10	4.5
	Fluoxetine	12	5.5
	Fluvoxamine	1	0.5
Atypical	Mirtazapine	54	24.5
TCA	Nortriptyline	13	5.9
	Imipramine	2	0.9
SNRI	Venlafaxine	16	7.3

Fourty eight (21.8%) were diagnosed as generalised anxiety disorder making it 2nd most common diagnosis. The other common diagnosis were obsessive compulsive disorder and somatoform disorder.

The most commonly prescribed drug in the study population were SSRIs. Among SSRIs, escitalopram and sertraline were most commonly used. Atypical antidepressant mirtazapine were the second class of drugs that we are prescribed to the study population after SSRIs.

Table 5 Showing type of adverse drug reactions in the studied population

Type of ADR		No.	Percent
Neurological	Sedation	92	42.2
	Insomnia	47	21.6
	Drowsiness	6	2.8
	Headache	81	37.2
	Dizziness	23	10.6
	Mental Confusion	28	12.8
	Amnesia	8	3.7
Metabolic/ Endocrine	Weight Gain	27	12.4
	Increased Appetite	86	39.4
	Anorexia	71	32.6
	Hyponatremia	11	5.0
	Raised Serum Cholesterol	1	0.5
	Raised Liver Enzymes	1	0.5
Gastrointestinal	Dry Mouth	118	54.1
	Nausea	107	49.1
	Constipation	60	27.5
	Epigastric Discomfort	40	18.3
	Diarrhoea	11	5.0
Psychiatric/ Behavioural	Irritability	55	25.2
	Restlessness	68	31.2
	Nervousness	21	9.6
	Auditory Hallucination	4	1.8
	Suicidal Ideation	1	0.5
Autonomic	Palpitation	57	26.1
	Excessive Sweating	22	10.1
Sexual	Delayed Ejaculation	10	4.6
	Impotence	6	2.8
Haematological	Leucopenia	5	2.3
	Agranulocytosis	1	0.5
Opthalmological	Blurred Vision	73	33.5
Others	Generalized Weakness	24	11.0
	Fatigability	21	9.6
	Running Nose	6	2.8
	Swelling of Lower Limb	2	0.9

Table 5 indicates the different types of ADRs reported by studied population. A total of 34 different types of ADRs were reported by the patients. A total of 1194 ADRs were reported by 207 patient dry mouth as the common (54.1%) ADR followed by nausea (49.1%), sedation (42.2%), increased appetite (39.4%), headache (37.2%) and blurred vision (33.5%). The most common organ system involved was gastrointestinal followed by neurological and psychiatric / behavioural. Other systems involved were autonomic, haematological, sexual, and ophthalmological. Eleven patients reported hyponatremia, 8 patients reports amnesia, 5 reported leucopenia while as 4 patients reported auditory hallucination as ADRs. Raised liver enzyme, raised serum cholesterol, agranulocytosis, and suicidal ideation were reported in 1% of the patients.

Table 6 Causality assessment according to WHO-UMC scale

Causality	No.	%age
Probable	152	73.4
Possible	48	23.2
Unlikely	7	3.4
Total	207	100

As per the WHO-UMC scale for assessing causality of ADRs, 152 (73.4%) were classified as probable, 48 (23.2%) were classified as possible and 7 (3.4%) were classified as unlikely.

Table 7 Showing ADR status in patients according to drugs used

Drug Used	ADR [n=207]		No ADR [n=13]		Total
	No.	%age	No.	%age	
Escitalopram	79	86.8	12	13.2	91
Mirtazapine	54	100.0	0	0.0	54
Sertraline	21	100.0	0	0.0	21
Venlafaxine	16	100.0	0	0.0	16
Nortriptyline	13	100.0	0	0.0	13
Paroxetine	10	100.0	0	0.0	10
Fluoxetine	12	100.0	0	0.0	12
Imipramine	2	100.0	0	0.0	2
Fluvoxamine	0	0.0	1	100.0	1
Total	207	94.1	13	5.9	220
P-value=0.005 ; Chi-square test (Exact p)					

The proportion of patients with ADRs varied with the drug used. Maximum proportion of patients with ADRs were reported with Escitalopram followed by Mirtazapine and Sertraline. The proportion of ADRs were 100% with Mirtazapine, Sertraline, Venlafaxine, Nortriptyline, Paroxetine, Fluoxetine and Imipramine respectively. There were no ADRs reported with the drug Fluvoxamine (100%)

Table 8 Showing association of ADR with age in studied population

Age (years)	ADR [n=207]		No ADR [n=13]		Total
	No.	%age	No.	%age	
11-20	24	88.9	3	11.1	27
21-30	45	93.8	3	6.3	48
31-40	53	93.0	4	7.0	57
41-50	50	96.2	2	3.8	52
51-60	19	95.0	1	5.0	20
>60	16	100.0	0	0.0	16
Total	207	94.1	13	5.9	220
P-value=0.742 ; Chi-square test (Exact p)					

Adverse drug reactions were the most common in the age group of above 60 years, followed by 41-50 years. There was however no statistically significant relationship between age and ADRs (p 0.742).

Table 9 Showing association of ADR with gender in studied population

Gender	ADR [n=207]		No ADR [n=13]		Total
	No.	%age	No.	%age	
Male	66	90.4	7	9.6	73
Female	141	95.9	6	4.1	147
Total	207	94.1	13	5.9	220
P-value=0.103 ; Chi-square test (Exact p)					

There was no statistically significant relationship between sex and the proportion of the ADRs (p 0.103).

Table 10 Severity of ADR in the study population according to the modified Hartwig and Siegel scale

Severity of ADR	No.	%age
Mild	190	91.8
Moderate	17	8.2
Severe	0	0.0
Lethal	0	0.0
Total	207	100

One hundred ninety (91.8%) of ADRs were mild in severity as per the modified Hartwig and Siegel scale. Only 17 (8.2%) of ADRs were moderate in severity. None of the ADRs belonged to severe or lethal category.

Table 11 Showing Severity of ADR according to drug used in studied population

Drug Used	Mild		Moderate		Total
	No.	%age	No.	%age	
Escitalopram	74	93.7	5	6.3	79
Mirtazapine	47	87.0	7	13.0	54
Sertraline	20	95.2	1	4.8	21
Venlafaxine	15	93.8	1	6.3	16
Nortriptyline	13	100.0	0	0.0	13
Paroxetine	9	90.0	1	10.0	10
Fluoxetine	10	83.3	2	16.7	12
Imipramine	2	100.0	0	0.0	2
Total	190	91.8	17	8.2	207
P-value=0.646 ; Chi-square test (Exact p)					

Adverse drug reactions moderate in severity were reported with the drugs like Fluoxetine, Mirtazapine, Paroxetine, Escitalopram, Venlafaxine and Sertraline. The ADRs due to Nortriptyline and Imipramine were exclusively mild in severity. In this study 93.7% of ADRs were mild and 6.3% of ADRs were moderate in severity due to drug Escitalopram which was most commonly prescribed drug.

Table 12 ADRs resulting into altered Biochemistry

ADRs with altered biochemistry	Drug causing the ADR	No.
Raised Liver Enzyme	Fluoxetine	1
Raised Serum Cholesterol	Venlafaxine	1
Agranulocytosis	Mirtazepine	1
Hyponatremia	Escitalopram, Mirtazepne	11
Leucopenia	Escitalopram	5

Out of a total of 1194 ADRs, 19 ADRs resulted in altered serum biochemistry including Agranulocytosis, raised liver enzyme, raised serum cholesterol, hyponatremia and leucopenia.

Summary

The present study was a prospective, observational study conducted by the Department of Pharmacology GMC Srinagar in collaboration with the psychiatry outpatient department of Institute of Mental Health and Neurosciences, Department of Psychiatry, GMC Srinagar between March 2015 to April 2016 with the aim of finding out the pattern of occurrence of adverse drug reactions among patients treated with antidepressants. WHO-UMC scale were used for causality assessment and modified Hartwig and Siegel scale was used to assess ADR severity. The mean age of the study population was 38.4 years and 66.8% of them were females and 33.2% of them were males. Major depressive disorder (60.9%) and generalised anxiety disorder (21.8%) were the most common diagnoses.

In our study SSRIs were more preffered drugs than other antidepressants. Among SSRIs, escitalopram are commonly used drugs followed by mirtazipine and sertraline respectively. A total of 1194 ADRs with 33 different types were observed in 207 patients, with an overall prevalence of about 94.1. All the reported ADRs were mild to moderate in severity according to modified Hart wig and Siegel scale. The most common reported ADRs were dry mouth (54.1%), nausea (49.1%), sedation (42.1%) and increased apeptite (39.4%). The most common organ system involved was gastrointestinal.

Most of the ADRs were found to be associated with the use of escitalopram followed by mirtazipine and sertraline. There was no statistically significant relationship between development of ADR with age (p=0.0.742) or sex (p= 0.103).

CONCLUSION

The present study showed only mild to moderate ADRs. The present study adds to the existing information on the pattern of occurrence of ADRs following antidepressant medication from the other centers where such studies have already been conducted and also create awareness among our own health care professionals about the importance of carrying out active surveillance studies regarding association of ADRs with various antidepressant drugs. Psychiatrists and other health care professionals treating psychiatric patients should have a good knowledge about possible ADRs following antidepressant medication and thus keep an active vigil to prevent, treat and alleviate the adverse health effects due to ADRs. The establishment of an active pharmacovigilance programme is hence an essential requirement to any health institution. This will help to gain more insight into the pattern of ADRs observed following different antidepressant medications and devise ways to identify and prevent adverse consequences due the ADRs. This will pave way to improve the quality of patient care by ensuring safer use of drugs.

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