original article

A prospective hospital based study to monitor the adverse drug reactions of antidepressant drugs in psychiatric department of a tertiary care hospital.

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Abstract

Background: Mental health has been hidden behind a curtain of stigma and discrimination for too long. Depression is the most common psychiatric illness of older people and is often undiagnosed. Antidepressant drugs carry the risk of untoward drug effects.

Objectives: The study was conducted to know the occurrence of various adverse drug reactions, to correlate the adverse drug reactions caused by antidepressant drugs with age and sex of patients and to assess causality of the reported adverse drug reaction.

Methods and Results : A total of 220 patients were monitored during the study period, out of those, 207 patients developed at least one or more than one ADR. A total of 34 different types of ADRs were reported by the study population. Majority of the ADRs were due to SSRIs. Escitalopram was widely prescribed and was also the most common drug implicated in causing ADR. Dry mouth was found to be the most common followed by nausea, sedation and increased appetite. The most common organ system involved is gastro intestinal followed by neurological and psychiatric/behavioral system. The present study showed only mild to moderate ADRs

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INTRODUCTION

Mental health has been hidden behind a curtain of stigma and discrimination for too long. The magnitude, suffering and burden in terms of disability and costs for individuals, families and societies are staggering. Mental health disorders are among the most common health conditions, directly affecting about a quarter of the population in any one year.[1] According to the World Health Organization (WHO), depression will be the second leading cause of global burden of disease by the year 2020.[2]

Depression is the most common psychiatric illness of older people and is often undiagnosed.[3] 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.[4] It is also an independent predictor of mortality.[5] Although effective treatment exists, depression is under-recognized and often under treated.[6]

Antidepressants are drugs which can elevate mood in depressive illness.[7] Antidepressants can reduce the symptoms of depression but their effect may also be unsatisfactory or lead to serious deterioration in the patient's condition.[8] Antidepressants are among the world's most frequently prescribed drugs. Their extensive use may partly be regarded as an expression of the increasing medicalisation of modern society.[9]

Four major classes of anti depressants are used to treat depression.

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KEY WORDS:
Anti depressants, Adverse drug reaction

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)
- Tricyclic Antidepressants (TCAs) / Tetracyclic antidepressants (TeCAs).

Although SSRIs are the most prevalent class of antidepressants used for depression, other classes of antidepressants may be prescribed instead.[10]

REVIEW OF RELATED LITERATURE

Jisha M Lucca, Ramesh Madhan, Parthasarathi Gurumurthy, Ram Dushad (2014) carried out a study to identify the prevalence and Severity of adverse drug reactions of antidepressant in a tertiary care teaching hospital. Patients prescribed with at least one antidepressant were randomly selected and monitored for adverse drug reactions (ADRs), irrespective of their age and gender. Of the 401 patients who received antidepressants, 170 patients (42.39%) experienced 204 adverse drug reactions. Selective serotonin receptor inhibitors (SSRIs) [110 (53.92)] was the most common therapeutic class of drugs associated with adverse drug reactions. [11]

Farhan Ahmad Khan, Kirti Vishwakarma, Vishal P. Giri, Chitrak Bansal (2015) analyzed the sleep disturbances as adverse drug reactions of various antidepressants prescribed to the patients attending psychiatry outpatient department (OPD). This prospective study was conducted on patients aged = 74 years attending Department of Psychiatry OPD and were prescribed Antidepressants for the duration of 8 months (December, 2013-July, 2014). The adverse drug reactions reported were confirmed by WHO UMC Causality Assessment Scale. Total number of patients enrolled on the basis of inclusion and exclusion criteria (n=50). Total number of adverse drug reactions related to drugs prescribed were found to be n=69. Total number of patients with sleep disturbances as adverse drug reactions were found to be 28. The drug most frequently implicated to cause sleep disturbances, was mirtazapine. Increased sleep was the most common adverse drug reaction found to occur. Unusual adverse drug reactions such as sleep talking was also seen.[12]

Shatavisa Mukherjee , Sukanta Sen , Seshadri S Chatterjee et al (2015) carried out a cross -sectional observational clinical study in the OPD of Psychiatry in Medical College , Kolkata . A total of 190 patients who received antidepressants were studied .5-8 consecutive previously diagnosed depression patients attending follow -up per day , were screened for suspected adverse drug reactions . A total of 190 patients were screened for the study of which males and females represented 43.68% and 56.31% of the cases respectively. The age -group presenting with maximum depressive problems was found to be 30-39 years. A total of 481 adverse drug reactions were noted of which dry mouth was the commonest closely followed by nausea and tremor . Out of 130 adverse drug reactions assessed for causality , 89.23% of the adverse drug reaction cases , were found to be 'probable while 10.77% were found to be possible. According to Hartwig and Siegel. 'Scale 83.99% of the cases were found to be mild ,14.97% moderate and 1.04% severe. The study enables to obtain information on the incidence and pattern of adverse drug reactions associated with antidepressants in the local population thereby reducing its occurrence and protecting the user population from avoidable harm.[13]

Priyanka Pravinbhai Hotha, Shilpa P. Jadav, Hiren R. Trivedi (2016) conducted a retrospective study from January 2011 to December 2014 and analyzed psychiatric hospitalized patients. Adverse drug reaction reports were assessed for probability, severity, psychotropic drugs involved and preventability. A total number of 101 adverse drug reactions were reported in 72 patients. Most common adverse drug reaction were mainly tremor 14 (13.86%), salivation 11 (10.89%) followed by muscle rigidity 6 (5.94%) and slurring of speech 6 (5.94%). In majority of the instances, it was antipsychotic agents 41 (56.94%) followed by antidepressants 11(15.27%) and mood stabilizers 11 (15.27%). As per causality assessment, 95 (94.05%) cases were 'possible' in WHO-UMC criteria and 72 71.28%) cases were 'possible' in Naranjo scale respectively. As per Schumock and Thornton preventability assessment, 91(90.09%) of total adverse drug reactions were in the not-preventable category. As per Hartwig and seigle's severity assessment, majority of adverse drug reactions 74 (73.26%) were mild in severity. They concluded that adverse drug reactions were most commonly associated with antipsychotic drugs. Developing an on-going adverse drug reaction reporting system with continuous motivation and creating awareness among the healthcare professionals for reporting suspecting adverse drug reaction will help to continue reporting and improving the patient's safety.[14]

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.

MATERIAL AND METHODS

After getting approval from the Institutional Ethical Committee, the prospective observational study was conducted by the Department of Pharmacology 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 not fulfilling the inclusion criteria.
2. Patient with severe psychiatric or medical illness such as acute psychosis, cardiac and hepatic failure.
3. Patients who are unable to cooperate.
4. 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.

Handling of adverse drug reaction reports

Adverse drug reaction were reported by active surveillance and a questionnaire was used asking the patient specific questions related to likely adverse drug reactions and patient's responses was recorded in the case record form. Once the adverse drug reaction reports were detected/collected and prepared in consultation with psychiatrist, nurses, pharmacists on duty in OPD, they were scrutinized to present any kind of reporting bias on part of investigator.

Causality Assessment

Following criteria was used for establishing causal relationship between drug administration and an adverse drug reaction:

1. A temporal (Time relate) relationship between suspected drug and adverse drug reaction.
2. Improvement after withdrawal of the drug i.e. positive dechallange.
3. A previous exposure to the same suspected drug i.e., pre challenge.
4. The lack of confounding effect i.e. adverse drug reaction is unlikely to be due to concomitant diseases or due to some other previously consumed medicines.

Based on above mentioned criteria adverse drug reactions are classified as under:

Definite:- Wherein adverse drug reaction followed a reasonable temporal sequence from administration of the drug and was confirmed by positive dechallange or positive rechallenge.

Probable:- Wherein adverse drug reaction followed a reasonable temporal sequence from administration of the drug, was confirmed by dechallenge but was not reasonably explained by the known characterization of patients clinical state.

Possible:- Wherein adverse drug reaction followed a reasonable temporal sequence from administration of the drug and followed a known response pattern to the suspected drug but could also have been produced by the patients clinical state or other modes of therapy administered to the patient.

Doubtful:- Adverse drug reaction that does not meet the above criteria especially if the adverse drug reaction has no temporal association with drug use.

OBSERVATIONS AND RESULTS

Table 1: Distribution of study population as per age

Age (years)	No.	%age
11-20	27	12.3
21-30	48	21.8
31-40	57	25.9
41-50	52	23.6
51-60	20	9.1
> 60	16	7.3
Total	**220**	**100**

Table 1 shows the age distribution of the study population. The mean age of the patients was 38.4 years with a standard deviation of 14.47 years. Most of

the patients were in the age group of 31 to 40 years (25.9%) followed by the age group of 41 to 50 years (23.6%).

Table 2: Distribution of study population according to residence

Residence	No.	%age
Rural	113	51.4
Urban	107	48.6
Total	**220**	**100**

Table 2 shows the distribution of study population according to the residence. 51.4% were from rural area and remaining 48.6% were from urban areas.

Table 3: Distribution of study population according to smoking status

Smoking Status	No.	%age
Smoking	31	14.1
Non Smoking	189	85.9
Total	**220**	**100**

Table 3 shows the distribution of study population according to smoking status.14.1% were smokers among the study group.

Table 4: Distribution of study population according to ADR

ADR	No.	%age
Present	207	94.1
Absent	13	5.9
Total	**220**	**100**

Table 4 signifies the distribution of the study population according to ADR. Out of 220 patients enrolled for study, 207 reported at least three or more ADRs. The prevalence of ADRs in the study population was 94.1%.

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 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

Out of a total 1194 ADRs, 149 (72%) were categorized as having a probable causal relationship with the antidepressant drug as per the Naranjo's monitoring scale. 53 (25.6%) were categorized as possible and the remaining 5 (2.4%) as doubtful as per Naranjo's scale.

Table 6: Causality assessment according to Naranjo's monitoring scale

Naranjo's score		No.	Total	%age
Doubtful	0	5	5	2.4
Possible	1	2	53	1.0
	2	5		2.4
	3	10		4.8
	4	36		17.4
Probable	5	129	149	62.3
	6	20		9.7
Total		207		100

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 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)					

SUMMARY AND CONCLUSION

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. Naranjo's monitoring scale and 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.

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