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A cross-sectional observational study on adverse drug reactions of anti-depressant drugs and compliance in the psychiatry outpatient department at Tertiary Care Hospital, Mumbai

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ABSTRACT

Adverse drug reaction is now seen as one of the major reasons for mortality and morbidity in the world. Moreover, these ADRs are under-reported and underestimated. Thus, the Pharmacovigilance program has been started to reduce the risk of ADR and the safety of drugs. Depression is the most common disorder affecting people of all ages, sex, socio-economic group and religion all over the world; it may range from a very mild condition, bordering on normality, to severe (psychotic) depression. This study may reveal the common drugs which may induce ADR's so that preventive care can be taken. Therefore the present study is planned to monitor, detect and analyze the adverse drug reactions of anti-depressant drugs in the Psychiatric Department. Aim and Objectives: Aim-To detects and analyze adverse drug reactions in patients with Depression and study patient's compliance in tertiary care hospitals. Objectives: Primary objective- To detect the types of ADRs induced by anti-depressant drugs and also estimate its incidence rate. Secondary objective- To assess the causality & probability of ADRs, To assess the severity of patients with respect to ADRs, To study the patient's compliance towards anti-depressant drugs. Methodology: Approval of Institutional ethics committee was taken prior to the initiation of the study. Enrolment of the patient was done as per inclusion and exclusion criteria. Only follow up patients were considered for our study to observe ADRs with the help of prescription copy. The hospital medical case record form of the patient was studied for the demographics, clinical history, clinical findings, diagnostic results and undergoing treatment and compliance. After total data collection from all patients, the ADRs were analyzed. A total of 200 patients were enrolled in our study. Males were 44% while females were 56%. 49 patients between 31 to 40 years, which was mostly found in this age group. Among all ADRs seen weight gain 4%, insomnia 19%, tremors 9.5%, fatiguability 0.5%, nausea 3.5%, sedation 2%, rash 3.5%, and other 4%. Further, the causality of ADRs was observed respectively by using the WHO-causality assessment scale. In which about 54.5% cases of ADR seen to be possible, while 31.8% were unlikely and 13% of ADR were conditional ADR. Naranjo's probability scale showed 69.6% of probable ADR while 30.3% of doubtful ADR. 82% of patients adhering to medication was measured by medication adherence rating scale while 18% were not adhering medication properly. Depression was seen mostly among people ranging from 31-40 years of age. Females were most affected by depression than the males. Among all the patients, Insomnia was mostly observed ADR in the patients. Other ADRs seen in patients were tremors, fatiguability, rash, weight gain, etc. Only possible and unlikely ADRs were found. Most of the patients were adhering to medication.

Keywords— *Depression, Anti-depressants, Adverse Drug Reaction and Compliance*

1. INTRODUCTION

The world health organization (WHO) defines an adverse drug reaction as a response to a drug that is noxious, unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for modification of physiological function. (WHO, 1972)

One among the leading cause of morbidity and mortality in the world is adverse drug reactions. World Wide ADRs stand on fifth rank among all causes of death. Epidemiological importance of ADR is justified by its high prevalence rate. They cause from 3% to 6% of hospital admissions at any type of age, and up to 24% in the elderly population. Due to increased physician visits and prolonged hospitalization. ADRs are a huge economic burden on patients. They represent from 5 to 10% of hospital costs. Adverse drug reactions may also result in diminished quality of life and increased health care costs. (R & G, 2011)

Reason for increase in morbidity and mortality due to ADRs are under-reported and underestimated. Lack of time and report form, and misconception of its importance are major reasons for under-reporting of ADRs. (Patel, *et al*., 2015)

To reduce the risk of ADRs and ensure the safer drug usage to patients all over the world the Pharmacovigilance Programs have been started. In India it is known by the Pharmacovigilance Programmed of India (PVPI), which runs under the Ministry of Health and Family Welfare, WHO defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects or any other drug related problems. (Verma, *et al*., 2014)

Depression is the most common of the affective disorders; it may range from a very mild condition, bordering on normality, to severe (psychotic) depression. Depression is common in all regions of the world. A recent study supported by WHO revealed that around 5% of people in the community had depression during the last year.(Mukherjee, *et al* 2017) It is an extremely common illness affecting people of all ages, gender, different socioeconomic group and religion in India and all over the world. It is significant contributor to the global burden of disease. These disorders often start at the young age; they reduce peoples functioning and often are recurring due to this reason. Depression is the leading cause of disability worldwide. (Jisha *et al.*, 2014)

Depression is one of the two diagnostic categories that constitute common mental disorder (CMDs), the other being anxiety disorder. It is most common disease due to that reason anti-depressant drugs are rapidly increasing. Anti-depressant drugs are effective to treat depression but they are not without any adverse effects. Hypotension, palpitation, anti-cholinergic effects, fatal arrhythmias, agitation, anxiety and insomnia were the common ADRs which were associated with the use of anti-depressant. (Swati, *et al*, 2013, Andiyappan)

Adverse drug reactions are important determinants of non-adherence to anti-depression treatment, but their assessment is complicated by overlap with depressive symptoms and lack of reliable self-report majors. (Swetha 2017) Treatment of depression is a long term therapy. Along with this the drugs can modulate the behavior changes and also leads to the suicidal behavior. Adverse drug reactions monitoring in the patients has various advantages for understanding safety of patient and efficacy of drug. The study of ADR may reveal the common drugs which may induced ADR's, so that preventive care can be taken. Also it was l help to focused on patients who are on suspected drugs. It gave as a choice to change the treatment and help patient to reduced ADR related health issues. In patients therefore present study was planned to monitor, detect and analyze the adverse drug reactions of anti-depressant drugs in Psychiatric department.

2. RATIONALE FOR STUDY

Depression is a very common disease in whole world and the use of anti-depressant drugs is rapidly increasing. Anti-depressant drug have many different type of ADRs. Agitation, anxiety and insomnia are the common ADRs which are associated with it. Very few studies have been carried out focusing on this aspect and our knowledge about the ADRs remains limited. Therefore this study was carried out with the aim to monitor, detect and analyze adverse drug reaction of anti-depressant drug in Psychiatric department.

3. STUDY HYPOTHESIS

Alternative hypothesis: There is significant numbers of adverse drug reactions seen in patient been treated with anti-depressants
Null hypothesis: There is no significant numbers of adverse drug reactions seen in patient been treated with anti-depressants

4. AIM AND OBJECTIVES

4.1 Aim

To detect and analyze adverse drug reactions in patients with depression and study patient's compliance in tertiary care hospital.

4.2 Objectives

Primary objective: To detect the types of ADRs induced by the anti-depressant drugs and also estimate its incidence rate
Secondary objective:

(a) To assess the causality & probability of ADRs.
(b) To assess the severity of patient with respect to ADRs.
(c) To study the patient's compliance towards anti-depressant drugs.

5. STUDY DESIGN

Study Type	: Cross-Sectional Observational Study
Study Site	: Department of Psychiatry, KEM Hospital, Parel, Mumbai.
Study Duration	: 3 Months.
Study Population	: Patients of OPD departments of Psychiatric, Parel, Mumbai.
Sample Size	: 197

6. SUBJECT SELECTION CRITERIA

6.1 Inclusion Criteria

(a) All patients who was diagnosed by major depression as per DSM V criteria
(b) Patients of both sexes were included.
(c) Patients had age 18years and above.

(d) OPD patients.
(e) Patients who were willing to give informed consent.
(f) Duration of treatment was minimally after 8 weeks.

6.2 Exclusion criteria

(a) Patients who were unable to communicate.
(b) Pregnant women.
(c) Patients with organicity.
(d) Patient who was taking treatment for medical co morbidity.
(e) Patient with psychotic symptoms.

7. SAMPLE SIZE CALCULATION:

Sample size determined by formula:

$$Sample\ Size = \frac{Z_{1-\alpha/2}^2\, p(1-p)}{d^2}$$

$Z_{1-\alpha/2}$= Standard normal variate (at 5% type 1 error (P < 0.05) it is 1.96.
p = Expected proportion in population based on previous or pilot studies.
d = Absolute error or precision.
So, Calculation:

$$Z_{1-\alpha/2} = 1.96$$
$$p = 15.1\% = 15.1/100 = 0.151$$
$$d = 5\% = 5/100 = 0.05$$

$$\text{Sample size (N)} = \frac{(1.96)^2 \text{ x } (0.151) \text{ x } (1- 0.151)}{(0.05)^2}$$
$$= \frac{3.8416 \text{ x } 0.151 \text{ x } 0.849}{(0.05)^2}$$
$$= \frac{3.8416 \text{ x} 0.1281}{0.0025}$$
$$= \frac{0.4924}{0.0025}$$
$$N = \mathbf{196.96}$$

So for this observational study at least 197 patients have to be taken.

8. STUDY METHODOLOGY

This was observational and cross-sectional study. This was conducted in compliance with the protocol, ICH GCP, Schedule 'Y' guidelines and Indian regulatory requirements. Approval of Institutional ethics committee was taken prior to initiation of study. Enrolment of patient was done as per inclusion and exclusion criteria. Before collecting the data or observing a prescription, signed dated written informed consent was taken from all subjects after providing them with patient information sheet. It was a cross-sectional observational study on adverse drug reactions of anti-depressant drugs and compliance in Psychiatry outpatient department at tertiary care hospital, Mumbai.

Only follow up patients were considered for our study to observing ADRs with help of prescription copy. The hospital medical case record form of patient was studied for the demographics, clinical history, clinical findings, diagnostic results and undergoing treatment and compliance. After total data collection from all patients, the ADRs were analyzed as per the following variable - causality, probability, severity of patient related to ADRs and compliance using WHO assessment scale, Naranjo's scale, clinical global impression and medication adherence rating scale respectively mentioned in the instruments. Formulated of result and conclusion was done at the end.

9. MATERIAL AND INSTRUMENT

Data was assessed by using the following scale and instruments:

(a) Semi - Structured Pro Forma: To document and record the socio-demographic details and Illness variables like Type Of Bipolar Disorder, Age of onset, Duration of Illness, number of episodes, number of hospitalizations, number of manic episodes, number of depressive episodes and treatment details (Drugs and ECTs).

(b) WHO-UMC Causality Assessment Scale: This is a practical tool based for the assessment of case report which is basically a combined assessment of clinical-pharmacological aspects of case history and also the quality of documentation of observation. It is six criteria tool which start from certain or probable of ADRs to unclassifiable or unassessable ADRs are used in Pharmacovigilance, to monitor unexpected and unknown adverse drug reaction.

(c) Naranjo's Probability Assessment Scale: This is scale has scoring system. It has 10 questionnaires which are answered Yes/No accordingly and based on total score we are able to find probability of ADR. If score is 0 ADR is Doubtful, For scoring 1-4 ADR is Possible, Between 5-8 it can be Probable and above 9 it is a Definite ADR**.**

(d) Clinical Global Impression (CGI): To measures illness severity, global improvement or change and therapeutic response Clinical global impression (CGI) is the format used. It is 7-point scale that ranges from normal to extremely ill patients and also ranges too much improve to getting worse after treatment. (Validity)

(e) Medication of adherence rating scale (MARS): It is a valid and reliable measure of adherence to psychoactive medications than both Drug Attitude Inventory (DAI) and the Medication Adherence Questionnaire (MAQ) and was developed by Dr

Katherine Thompson. It is a set of 10 questionnaires with has to answer by patient by Yes or No which describes their attitude towards medication and their behaviour.

10. RESULT

A total 200 patients were observed during this study. Patients having multiple types of ADRs. Total of 94 (47%) ADRs were observed. Out of 200 patients, males represented 44% of the cases and while females represented 56% of the cases. (Show in fig. no. 1) During this study we observed most of the patients are diagnosed by depression in between age group of 31-40, that is 27.2%. Most of the ADRs were observed in age group of 31-40.

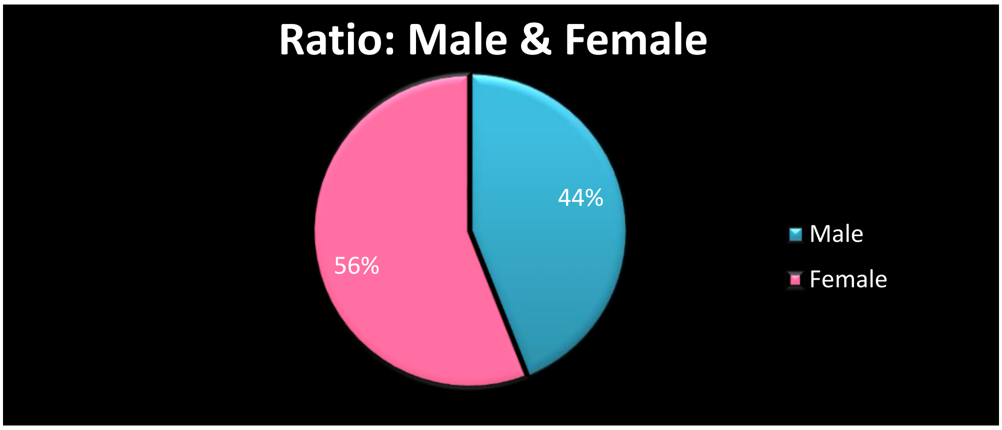

Fig. 1: Graphical representation of Male and Female Ratio

Age of distribution showed 4 patients age were less than 20years, 27patient were between 21 to 30years of age, 49 patient were between 31 to 40 years, 46 patient were between 41 to 50years age, 51 to 60 years age had 36 patient and 38 patient were above 60 years age. (Show in figure 2)

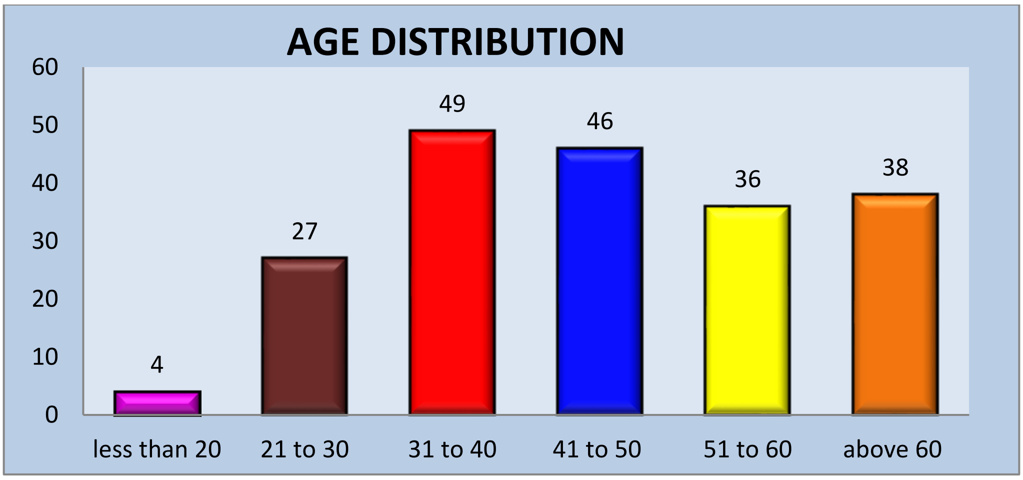

Fig. 2: Graphical representation of Age Distribution

Among all ADRs seen weight gain 4%, insomnia 19%, tremors 9.5%, fatiguability 0.5%, nausea 3.5%, sedation 2%, rash 3.5%, and other 4% respectively. (Figure 3)

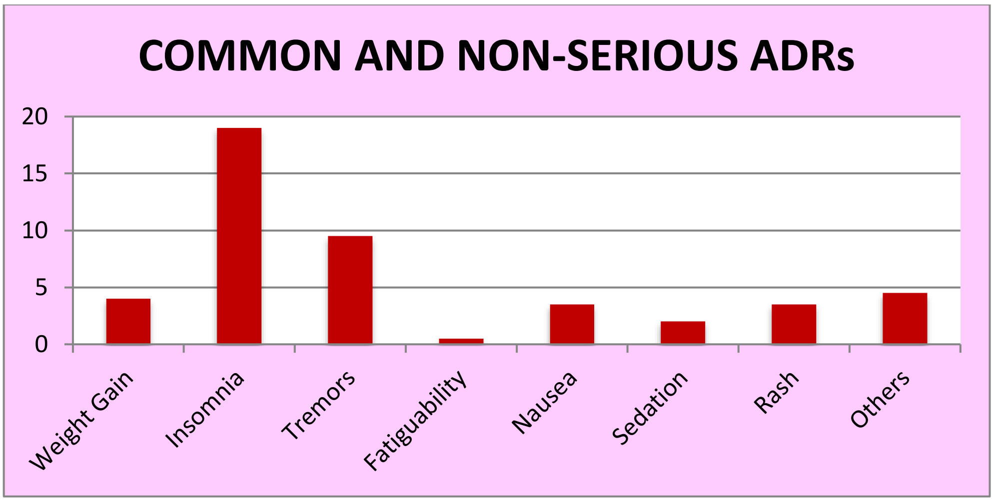

Fig. 3: Graphical representation of Types of ADR

Table 1: Age wise distribution of number of ADRs with respect to group of drugs

Sr No.	Age Group (In Years)	No of Male	No. of Female	No of ADRs Observation	Group of Drugs
1	less than 20	1	0	01	Anti-psychotic drugs
2	21 to 30	2	6	08	Anti-psychotic drugs, Anti-depressant drugs, Anti-epileptic drugs
3	31 to 40	8	10	18	Anti-psychotic drugs, Anti-epileptic drugs, Anti-psychotic drugs
4	41 to 50	9	7	16	Anti-depressant drugs, Anti-psychotic drugs, Sedative & Hypnotics
5	51 to 60	4	7	11	Anti-depressant drugs, Anti-psychotic drugs, Anti-epileptic drugs, Sedative & Hypnotics
6	Above 61	3	9	12	Anti-epileptic drugs, Anti-depressant drugs
Total		27	39	66	

In above table, One ADR observed was in male patient of less than 20 years. This suspected group of drug is Anti-Psychotic drug. For between 21 to 30 years, total 8 ADRs were seen in 2 males and 6 females. Suspected group of drug was Anti-Psychotic drug, Anti-Depressant and Anti-Epileptic drug. In age group of 31 to 40, Total 18 ADRs were seen in 8 males and 10 females. Suspected group of drugs were Anti-Psychotic, Anti-Epileptic drugs. In between 41 to 50 age group total 16 ADRs were observed in 9 males and 7 females. Suspected group of drugs were Anti-Depressant, Anti-Psychotic, Sedative and Hypnotics drugs. Total 11 ADRs were observed in age group between 51 to 60, in 4 males and 7 females. Suspected group of drugs were Anti-Depressant, Anti-Psychotic, Anti-Epileptic, Sedative and Hypnotics drugs. Also 12 ADRs were observed in above 61 years patients, 3 in males and 9 in females. Suspected group of drugs were Anti-Epileptic, Anti-Depressant drugs.

Further, causality of ADRs is shown in figure 4 by using WHO-causality assessment scale. In which about 54.5% cases of ADR seen to be possible, while 31.8% were unlikely and 13% of ADR were conditional ADR.

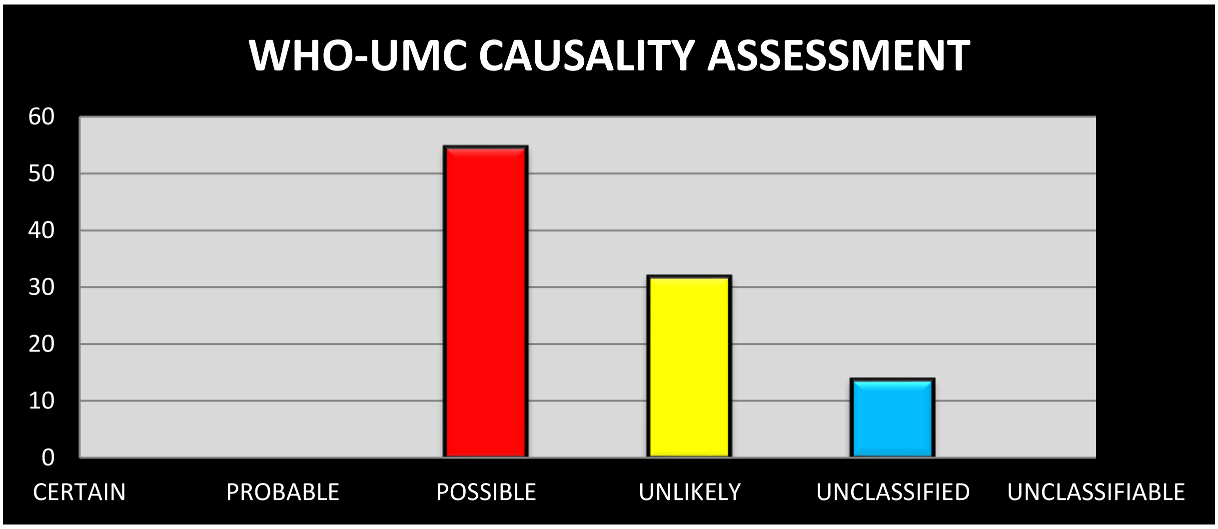

Fig. 4: Graphical representation of WHO-causality assessments scale in percentage

Naranjo's probability scale showed 69.6% of probable ADR while 30.3% of doubtful ADR which is shown in fig no. 5. In our study we don't found any definite and probable ADRs.

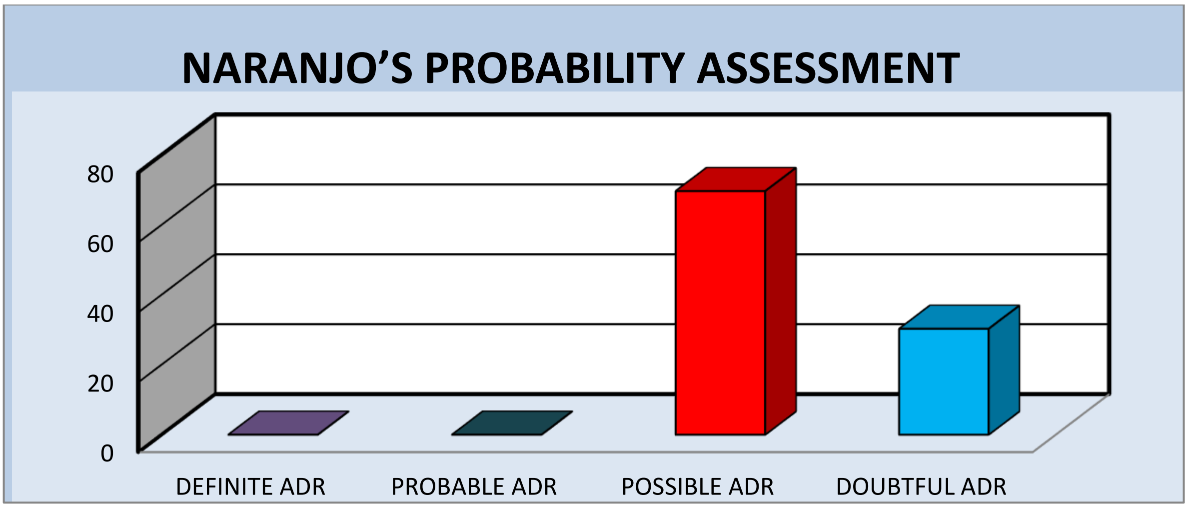

Fig. 5: Graphical representation of Naranjo's probability assessment in percentage

Clinical global impression measured severity of patient among which show in figure 6, Percentage of patient normal, not at all ill is 24.5%, 32.5% were borderline ill, 26.5% were mildly ill and 15.5 % were moderately ill.

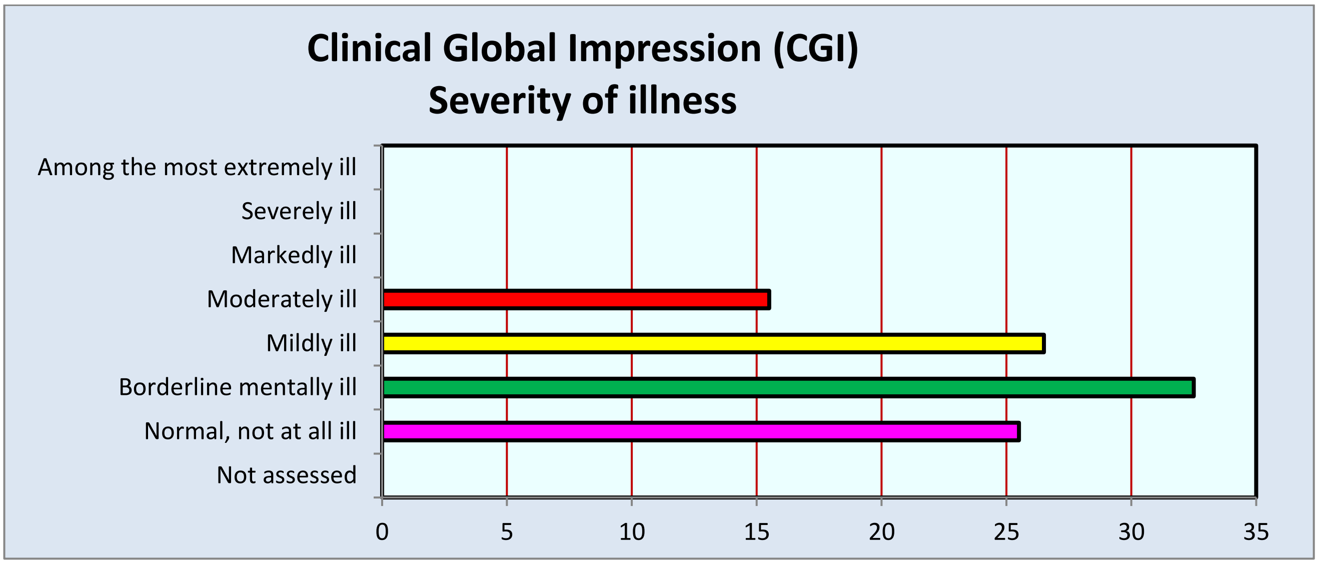

Fig. 6: Graphical Representation of Clinical Global Impression measured Severity of patient's illness

Clinical global impression for improvement of patient showed in figure 7 that is17.5% patient are very much improved, 54.5% are much improved, and 28% are minimally improved.

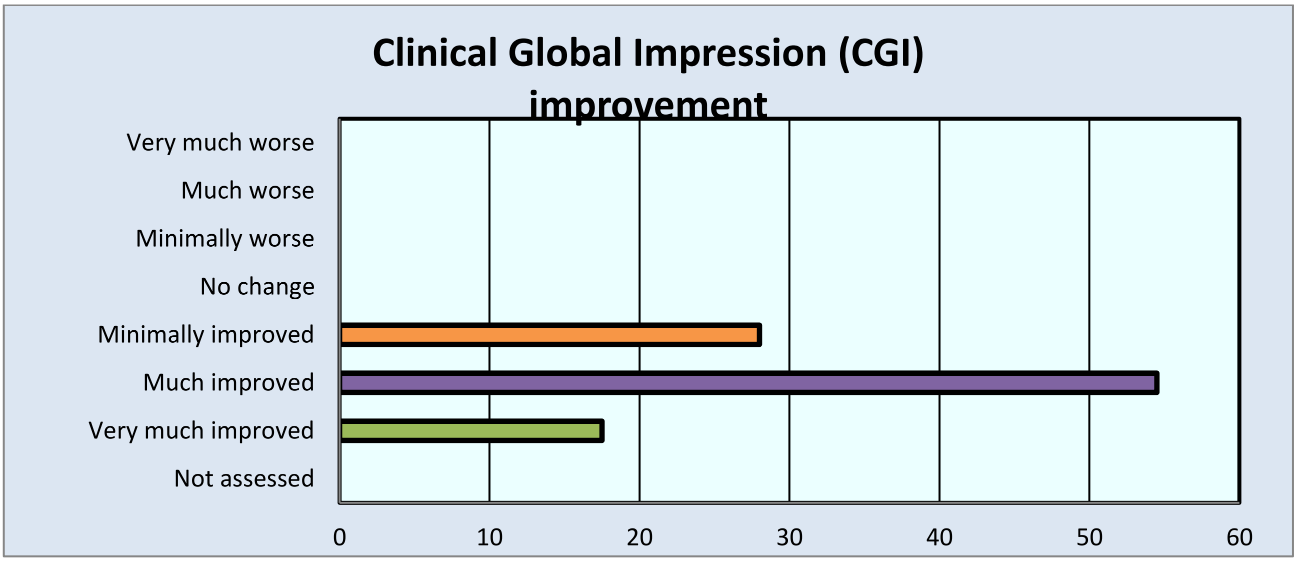

Fig. 7: Graphical representation of Clinical global impression for Improvement of patients

82% of patient adhering to medication was measured by medication adherence rating scale while 18% were not adhering medication properly which is mention in figure 8.

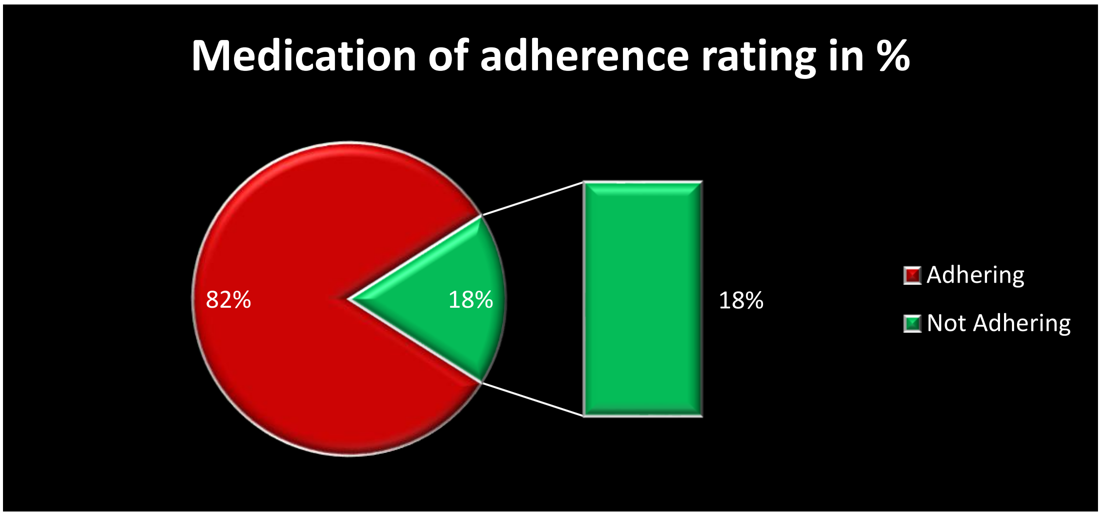

Fig. 8: Medication of adherence rating in percentage

11. DISCUSSION

This was crosssectional observational study on adverse drug reactions of anti-depressant drugs and compliance in depression patient under psychiatry outpatient department in tertiary care hospital, Mumbai. Main focus of this study was to find adverse drug reaction of antidepressant and compliance. Number patient seen with depression were 77, while other patient were major depressive disorder (67), depression with anxiety(34),depression with panic attack (5), depression with psychotic features (3), post-psychotic depression(3), depression with OCD(2), mild depression (1), depression with somatization(1), depression with resistance (1), depression with mood coagulant and psychotic features (1),depression with schizophrenia (1), double depression (1), MDD with somatic compliance (1), MDD with psychotic features (1) and MDD with panic attack(1). In this study, 66ADRs were seen out of 200 patients showing 33% of prevalence rate. This prevalence rate is similar to study "Prevalence and Severity of Depression and Its Association with Substance Use in Jimma Town, Southwest Ethiopia" done in 2015 having 29% as prevalence rate. In present study males ware observed 44% and Females were observed 56%, Females are more affected than the males. Types of ADRs sense among patient were weight gain (4%), insomnia (19%) which one of the mostly observed in the patients, then tremors (9.5%), fatiguability (0.5%), nausea (3.5), sedation (2%), Rash (3.5%) while 4.5% were classified as others, all of these were common and non-serious ADRs.

Related study was conducted by Swati T et al, They considered total 160 cases for ADRs by using a predesigned CDSCO form. They assessed causality by using the criteria of WHOUMC. The study states that agitation, anxiety and insomnia are the common ADRs which are associated with the use of antidepressants. In the present study no any serious ADR was observed. Among the total ADRs seen 54.5% of patients were classified as possible, while 31.8% were unlikely and 13.5% of them are conditional/ unclassified by used the WHO causality assessment scale. Study was further assessed with its probability of ADRs by using Naranjo's probability scale in which 69% of patient had possible ADRs and 31% of patient had doubtful ADR. Our study had no any certain and probable ADRs case was found. This is in contrast study to a Shatavisa Mukharjee et al, that resulted were patients who presented with a total of 130 ADRs could be assessed for causality using Naranjo's scale—for 116 of those ADRs, the causality was 'probable'; for the rest 14, it was 'possible'. Our study had no 'certain' cases as re-challenge was not attempted by the attending physician, once a drug was withdrawn. In this study, clinical global impression was used to measure severity of patient having 25% as average and 4.2 as standard deviation from range of 1 to 4. Further clinical global impression was helpful to find improvement of patient showing 33% as average and 3.2 as standard deviation from range 3 to 6. Then study was further showed that 82% of patient were adhering medication timely while only 18%patient were not taking their medication timely. Another outcome of this study was duration since percentage of patient were taking medication from 0-5years was 63.5%, 18.5% of patient were showing 6 to 10years of duration of treatment whereas 9% of patient each took treatment for 10-15 and 15 and above years.

12. CONCLUSION

Females were most affected by the depression than the males. Most of the people cause depression due to the family problems. Among all the patients Insomnia was mostly observed ADR in the patients. Only possible and unlikely ARDs were found. Not any serious ADR caused in patients due to antidepressant drugs. Most of patients were borderline mentally ill at the starting level but after they started antidepressant drugs patients gets much improved. Most of the patients were adhering to medication. Patients taking anti-depressant drugs for the long time.

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