

A PROSPECTIVE STUDY TO EVALUATE THE PREVALENCE OF ADVERSE DRUG REACTIONS AND ITS IMPACT ON QUALITY OF LIFE IN PSYCHIATRIC PATIENTS AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Background: Because of the rise in reported adverse drug reactions (ADRs), there is a greater focus on pharmacovigilance (PV) these days.

The backbone of treating mental patients, psychotropic medicines are associated with a number of adverse drug responses. The focus of the current investigation is on identifying the pattern of adverse drug reactions (ADRs) associated with antipsychotic and antidepressant treatment. The purpose of this research is to ascertain the frequency of adverse drug reactions (ADRs) and how these reactions affect patients' quality of life (QOL) after an ADR. **Methodology:** Using antipsychotics and/or antidepressants, 300 participants in all were included in this prospective observational research. They underwent screening to rule out any ADRs. Additionally, potential risk factors for the emergence of ADRs were evaluated. Patients who were taken antidepressants (ADs) or antipsychotics (APs) showed a distinct pattern of adverse drug reactions (ADRs).

It was determined how many APs and/or ADs were prescribed on average. The World Health Organization-Uppsala Monitoring Center (WHO-UMC) scale, Naranjo's algorithm, and Hartwig-Siegel scale were used to evaluate the causation and severity of the detected ADRs,

respectively. Finally, the effect of ADRs on the quality of life of patients on APs and/or ADs was assessed. **Findings:** 24.33% of patients getting APs and/or ADs had an adverse drug reaction. The most often given AD is sertraline, while the most often prescribed AP is olanzapine. The two drugs with the greatest number of ADRs as AP and AD, respectively, are olanzapine and sertraline. It has been shown that women are more likely to have ADRs. Polypharmacy and several comorbidities are also thought to be potential risk factors. 1.94 prescriptions for APs and/or antidepressants are filled on average. When compared to ADs, APs are considered to be more accountable for ADRs. The highest number of ADRs is within the parameters that the WHO-UMC scale and Naranjo's algorithm may use to determine causation. According to the Hartwig-Siegel severity scale, all of the recorded ADRs are classified as mild or moderate. The physical and psychological domains of QOL evaluation are significantly impacted by ADRs.

Conclusion: This study's findings demonstrate the importance of photovoltaics. Enhanced awareness and rigorous monitoring may help lower the incidence of adverse drug reactions (ADRs) in patients on psychiatric drugs. Thus,

there might be a decrease in the negative effects of ADRs on patients' quality of life.

Keywords: pharmacovigilance, quality of life, psychiatry, adverse medication responses, and psychotropic pharmaceuticals.

I. INTRODUCTION

World Health Organization defines mental health as a state of well-being in which every individual realizes their potential, can cope with the normal stresses of life, and can work productively and fruitfully.[1] Mental disorders are characterized by some combination of abnormal thoughts, emotions, behavior changes, and many more.[2] Many people have mental health concerns from time to time. But it becomes a mental illness when ongoing signs and symptoms affect your ability to function. These symptoms can be managed with a combination of medications and psychotherapy. Antipsychotics are a group of medications that are used mainly for the treatment of mental disorders. Antidepressants are a type of medications that are used to treat or relieve symptoms of clinical depression and various other conditions like anxiety disorders, obsessive-compulsive disorder (OCD), and so on.[3-6] Adverse drug reaction (ADR) is a response to a drug that is noxious, unintended, and occurs at doses normally used in humans for the prophylaxis, diagnosis, treatment of disease, and for modification of physiological function.[7] Errors in drug administration or compliance, therapeutic failures, accidental poisoning, and drug abuse do not fall under this definition. Psychotropic drugs are available plentiful and their use is increasing day by day. These drugs can cause several ADRs, some of which can be fatal.[8-10] Due to the association with a high number of ADRs with psychotropic drugs, it leads to noncompliance and discontinuation of therapy. Thus, monitoring the safety profiles of psychotropic drugs is essential.

Pharmacovigilance (PV) is helpful in the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. It includes ADR monitoring as one of its activities which involves the detection and assessment of adverse effects.[9,11,12] Effective management of these unwanted effects of APs has the potential to improve patient compliance, quality of life (QOL), and possibly the prognosis and outcome. Effective monitoring and working on this aspect can help physicians prevent adverse effects.[13,14] The ADRs due to psychotropics are also known to have a significant impact on morbidity, mortality, health-care costs, and compliance of the patient.[7] From the previous study, the prevalence of ADR (s) in patients taking APs and ADs was found to be in the range of 10.2–22.8%, while in India the range varies from 0.69% to 41.9%.[14-17] Few studies have been carried out in India as well as in Gujarat on studying the prevalence of ADRs and their effect on the QOL

Table 1: Age group distribution

Age	No. of patients	Percentage (%) of patients
18-30	102	34.00
31-50	144	48.00
51-70	50	16.67
>70	4	1.33
Total	300	100.00

Table 2: Risk factors in patients with ADR					
	Patients with ADR (n=32)	Percentage (%)	Total patients (n=300)	Percentage (%)	ADR prevalence
Gender					
Male	46	54.79	179	59.67	22.33
Female	33	45.21	121	40.33	27.37
Age					
18-30	23	58.77	102	34.00	29.59
31-50	46	54.79	144	48.00	27.78
51-70	11	13.07	50	16.67	22.80
>70	1	1.17	4	1.33	25.00
No. of comorbidities					
Singla	9	22.23	50	16.67	18
Double	10	23.7	15	11.67	29.57
Multiple	3	6.11	8	3	33.33
No. of medications					
<3	3	6.11	27	9.00	11.11
3-5	42	94.09	243	80.67	23.57
>5	4	10.06	10	3.33	80.00

of the patients.[17] In recent years, the measurement of health indicators such as mortality, morbidity, and QOL has turned into an important outcome for clinical studies.[18,19] Recently, many methods have been developed to determine QOL in various groups. One of these methods is the World Health Organization

QOL-BREF (WHOQOL-BREF) questionnaire. It is used to capture many subjective aspects of QOL. It is one of the best-known methods that has been developed for comparisons of QOL, also available in many languages. This method, by focusing on individuals' views of their well-being, provides a new perspective on life.[20-23] However, it is the risk–benefit ratio of the drugs that matters.

Need of study:

APs and ADs are the most frequently prescribed drugs among psychiatric patients. They are also associated with the risk of causing ADRs which are often neglected. Underreporting (UR) of ADRs is a widespread and daunting challenge in PV. This is because primarily most countries, including India, follow the spontaneous or voluntary system of ADR reporting. There are patient-related reasons for UR like failure to recognize ADR or inability to link ADR with a drug. The commonest doctor-related reasons are the feeling of guilt, fear of litigation, ignorance, lethargy, inadequate risk perception about newly marketed drugs, insufficient training to identify ADRs, and lack of awareness about PV programs. Thus, ADRs often go unnoticed. Very few studies have been carried out to find the prevalence of ADRs due to psychotropic drugs and to assess their impact on the QOL of psychiatric patients in our settings. Thus, in this study, we aim to report the prevalence of ADR and its effects on QOL using the WHOQOL-BREF-QOL scale.

II. METHODOLOGY

This was a prospective observational cross-sectional study conducted for 6 months in the Department of Psychiatry, Dhiraj General Hospital, Vadodara. The study was initiated after getting approval from Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC/ ON/Phar/BNPG16/D17004, date: 13/12/2017). All patients of either gender or age

≥18 years that visited or were admitted to the department of psychiatry were reviewed and the patients who experienced an ADR (s) and fulfilled the inclusion criteria were enrolled in the study; after explaining to the patients the details of the study, the Informed consent form (ICF) was taken. All the relevant data were obtained from the patients' medical records and through counseling the patients who visited the out-patient department (OPD) or in-patient department. They were screened for possible ADRs. Possible risk factors for the development of ADRs were also assessed. The difference in the pattern of ADRs in patients prescribed with ADs and/or APs was observed. The average number of APs and/or ADs per prescription was calculated. The causality and severity assessment of the observed ADRs were done by the WHO-UMC scale, Naranjo's algorithm, and Hartwig–Siegel scale, respectively. Lastly, the impact of ADRs on the QOL of the patients receiving APs and/or ADs was evaluated. After the data collection, all the data were exported to statistical software for statistical analysis. All the quantitative data were represented in percentage (%) and mean ± standard deviation. Comparative statistical differences were calculated using appropriate parametric tests. The categorical data represented in the median and comparative statistical differences were calculated by using appropriate non-parametric statistical tests (Chi-square test and independent t-test). The graphical representative was used for a better understanding of the data. A P value of ≤0.550 was considered significant.

III. RESULTS

A total of 300 patients were included in the study according to the inclusion and exclusion criteria. Out of 300 patients, 24.33% (N = 73) patients were affected by ADRs irrespective of their severity. We noticed that the number of patients hospitalized for further treatment was

just 6% (N = 18) as compared to the patients who visited the OPD was 94% (N = 282). Comparing the gender proportionality, male represents 60% (N = 179) while female represents 40% (N = 121) of the population. In our study, the age of patients varies from 18 to 80 years with a mean age of 38.09 ± 13.51 years. The maximum number of patients were from the age group of 31–50 years [48% (N = 144)] followed by the age group 11–30 years [34% (N = 102)], and lastly, the least number of patients [1.33% (N = 4)] were found in the age group of >70 years. [Tables 1 and 2] Patients were diagnosed according to the signs and symptoms of the illness as well as the laboratory investigations. In our study, we noted that the maximum number of patients were diagnosed with mental depression disorder (MDD) comprising 29.67% (N = 89), bipolar mood disorder (BMD) with 18.37% (N = 55), psychosis with 16.67% (N = 50), anxiety with 11.67% (N = 35), and schizophrenia with 10% (N = 30) of the total population. Various minor diagnoses included alcohol use disorder with 3.67% (N = 11) and sleep disorder with 3% (N = 9). Other diagnoses included functional neurological system disorder, insomnia, OCD, seizure, panic disorder, conversion disorder, and nicotine use disorder with 7% (N = 21) [Figure 1]. According to the suspected diagnosis, medications were prescribed which contain APs and/or ADs. We reviewed the prescriptions and noted that the patients received 1.94 (mean) of APs and/ or ADs per prescription. Sixty-three percent (N = 252) patients were prescribed with at least two APs and/ or ADs in prescription. There was 15% (N = 45) with three while 0.67% (N = 2) with four APs and/or ADs prescribed. APs were prescribed for 37.33% (N = 112) male patients and 18.00% (N = 54) female patients, while ADs were prescribed for 22.33% (N = 67) of both male and female patients. The most

prescribed APs were olanzapine in 35.67% (N = 107) of patients and ADs were sertraline in 22.33% (N = 67) of patients [Figure 3].

Out of 581 APs and ADs prescribed, 76.25% (N = 443 times) answer was “NO” for the suspected ADRs of drugs and 23.75% (N = 138 times) answer was “YES” for suspected ADRs of drugs. Considering the number of patients suspected of ADRs caused by APs and ADs, 75.67% (N = 300) of patients did not suffer from any ADR [Figure 2]. Not only the ADRs were identified but also the possible risk factors were determined. Considering the gender distribution in patients suffering from ADRs, 27.27% of females suffered from ADRs out of the total female population, while 22.35% of males suffered from ADRs out of the total male population in the study. The average age of the patients suffering from ADRs was 38.09 ± 13.51 years; 27.78% of the total population under the 31–50 age group suffered from ADRs and 80% of the total population that was prescribed more than five drugs were found to have ADR (s). The average number of medications prescribed in the subjects with ADRs was 3.56 ± 0.92 . The maximum proportion of ADRs found in groups of subjects with multiple comorbidities is 33.33%, followed by subjects with two comorbid diseases 28.57% out of the total subjects in that group. After the prescription was examined, we interviewed the patient and screened for ADRs. A list of suspected ADRs for prescribed APs/ADs and classified into systemic classes is listed in Table 3. ADRs of APs that were categorized in the psychiatric system were 9.81% (N = 57 times), neurological was 11.53% (N = 67 times), metabolic was 4.65% (N = 27 times), gastrointestinal was 11.53% (N = 67 times), and others were 18.93% (N = 110 times). While ADs that affected the psychiatric system were 8.26% (N = 48 times), neurological was 9.29% (N = 54 times),

metabolic was 2.58% (N = 15 times), gastrointestinal was 8.78% (N = 51 times), and others were 14.63% (N = 85 times). Considering the occurrence of ADRs due to APs, 14.29% (N = 83 times) are affected and olanzapine was the drug with the highest number of ADRs—26.33% (N = 153 times), while in ADs ADR occurrence was 9.47% (N = 55 times) and escitalopram had the highest number of ADRs—12.56% (N = 73 times) as demonstrated in Table 4 and Figure 5.

Causality assessment by both WHO-UMC Causality Assessment and Naranjo’s Algorithm was performed. By WHO-UMC Scale, the majority of ADRs were found to be “Possible” with 65.48% (N = 385 times). There were no cases of certain. As per Naranjo’s Algorithm, the majority of ADRs were found to be “Possible” with 90.65% (N = 533 times) [Figures 6-8]. There were no cases of definite. The severity assessment of the major ADRs was carried out amongst which Parkinsonism, seizures, and Extra pyramidal side effect (EPS) were classified to be moderated according to Hartwig–Siegel scale as mentioned in Table 5. After the assessment of ADRs, we found 19 patients with major ADRs (i.e., tremors, extrapyramidal symptoms, seizures, sensation in hands, and Parkinsonism) out of which 14 were males and 5 were females. They were included in the QOL analysis which was performed according to the WHOBREF-QOL Questionnaire. This was further classified into four domains: physical, psychological, social, and environmental as described in Table 6. The patient’s pre-data were noted according to the patient’s perception before the occurrence of ADR and post-data were noted at the time the patient reported the ADR. Then, we calculated the difference between the pre-data and post-data of raw score and transformed score (i.e., 4–20, 1–100). More importantly, we found that after the QOL

Assessment, comparing the mean value of pre- and post-data, the value of post-data decreased in all four domains. For the significance of data, we use Chi-square test for statistical analysis. This decrease in mean of post-data was significant (P-value< 0.05; CI 90%) in physical and psychological domains, while the decrease in mean was not significant (P-value< 0.05; CI 90%) in social and environmental domains. Moreover, we noted the mean difference between pre- and post-data of males and females in all domains. In physical domain, it was 4.28 in males and 5.14 in females, while in the psychological domain, it was 4.25 in males and 3.96 in females. Similarly, in the social domain, it was 0.34 in males and 0.72 in females. However, in the environmental domain, it was 1.05 in males and 1.50 in female [Figures 9 and 10].

IV. DISCUSSION

In psychiatry, the frequency and severity of ADRs play an important role in the effectiveness and tolerability of the drugs and are the major contributors to noncompliance and reduction of QOL. ADRs can even

Table 3: Classification of ADRs according to system

Psychiatric	Neurologic	Metabolic	Gastrointestinal	Other
Abnormal	Alcoholism	Anorexia	Abnormal taste	Blurred vision
Drowsy	EPH	Insomnia	Constipation	Adverse
Anxiety	Headache	epstein	Diarrhea	Back pain
Change in smell	Ligh	Nausea	Dyspepsia	Chest pain
Neckle stiffness	Insulinism	Weight	Heartburn	Chilly
Depression	Pain	gale	Stomach	Itching
Incontinence	Parkinsonism	Diarrhea	Soremouth	Dizziness
Irritability	Redness leg	epstein	Dry mouth	Mouthless
Lethargy	redness	Weight loss	Abdominal pain	Fatigue
Lidiate decrease	Seizure			Fever
Night vision	Shard			Twitching
Sedation	speech			Yawning
Sleep problems	Twitching			Hot/coldness
Somnolence	Vertigo			Stuck pain
Decreased concentration	Nervousness			Sweating
Apathy	Rednessness			Weakness
	Tremor			Shoulder pain
				Arterial hypertension
				Urinary frequency
				Shaking
				Flu like syndrome
				Sensation in hands

Table 4: Comparison of ADRs among APs and ADs prescribed

Drug prescribed	Total no. of times prescribed	Occurrence of ADR	Percentage (%)
AP	293	83	14.29
AD	288	55	9.47
Total	581	138	23.75

Table 5: Severity of ADRs

ADRs	No. of patients	Percentage (%) of prevalence	Severity
Tremor	15	5.00	Mild
Parkinsonism	1	0.33	Moderate
Sensation in hands	1	0.33	Mild
Seizures	2	0.67	Moderate
EPS	3	1.00	Moderate

be a source of burden on the patients, their caregivers, and the health-care system.[14] In our study, we included 300 patients who were on APs or ADs due to various psychiatric illnesses. Male patients encountered were more than female patients at a ratio of 3:2, respectively, in concordance to the study carried out by Shah et al. [24] and Gummadi et al. [25] The mean age of the subjects was 38.09 years. The majority of patients were diagnosed with MDD in 18% of females and 12% of males, followed by BMD in 4% of females and 14% of males, while psychosis in 5% of females and 11% of males. We also examined the number of APs or ADs prescribed per patient. Patients received 1.94 ADs and/or APs per prescription. Some patients were also on concomitant other medications for epilepsy, sleep disorders, anxiety, hypertension, and some of the Over the counter (OTC) medications for cough or some minor illnesses. The history of such subjects was carefully considered before attributing ADRs to APs and ADs to rule out any possible cause of ADR due to medications other than APs and ADs. Olanzapine was the maximum prescribed antipsychotic, while sertraline was the maximum prescribed antidepressant in our setting. Overall, the most commonly prescribed drugs were olanzapine, sertraline, venlafaxine, and aripiprazole. Out of 300 subjects, 73 subjects

developed ADRs including 40 males and 33 females. Overall, the incidence rate of ADRs found in this study is 24.33% which is higher than the result found in the study carried out by Munoli and Patil[26] (5.2%), lower than that of the study conducted by Lucca et al. [14] (34.24%) and Shah et al. [27] (32.8%). Risk factor assessment showed that the prevalence of ADRs was more in females in comparison with males like the observations of Gummadi et al. [25] in his study and in contrast to results found by Munoli and Patil.[26] It is well reported in various studies that ADR are more common in females than in males. That can be due to various reasons like gender-related changes in pharmacokinetics, pharmacodynamics, pharmacogenetics, immunological, and hormonal factors as well as differences in the use of medications (contraceptives) by women compared with

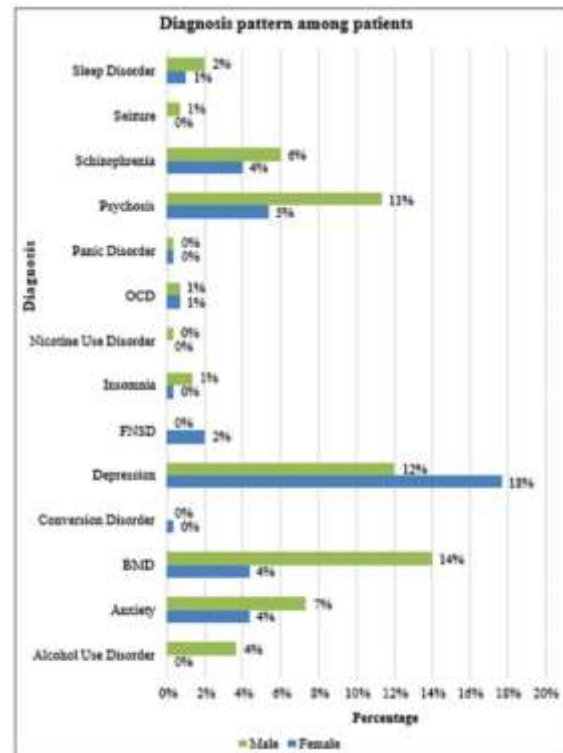


Figure 1: Diagnosis pattern among patients

men. Patients in the age group of 31–50 years had the maximum number of ADRs. Similar results are observed in the studies conducted by.[23] and Lucca et al. [14] But it is in contrast to the well-established fact that geriatric patients are more prone to ADRs as seen in studies lead out by Mandavi et al. [28] and Alomar.[29] However, the number of geriatric patients encountered was also less.

Comorbidities and the number of drugs consumed by the subject are interrelated. An increase in comorbidities leads to increased drug consumption. Comorbidities can also lead to various pathophysiological changes in individual patients. ADRs were found to be maximum in subjects with multiple comorbidities. This result is following the result obtained in the study done by Mandavi et al. [28] Polypharmacy can lead to poor compliance, drug interactions, adverse drug reactions, underuse of effective treatments, and medication errors. The occurrence of ADRs was found maximum in the patients where more than five drugs were prescribed per prescription. Thus, polypharmacy can be considered a possible risk factor for the development of ADRs. Many studies have evidence for polypharmacy to be a risk factor. The most common ADR was found to be a headache which differs from the results of the study carried out by Shah et al. [24] in which asthenia is found

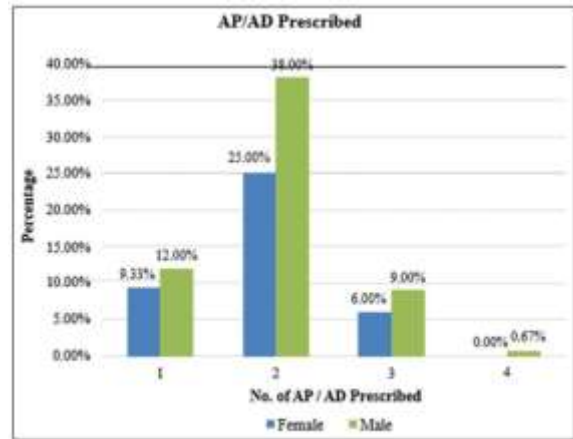


Figure 2: No of APs and ADs prescribed per patient

Domain	Facets incorporated within domains	
1. Physical health	Activities of daily living	Mobility
	Dependence on medicinal substances and medical aids	Pain and discomfort
	Energy and fatigue	Sleep and rest
		Work capacity
2. Psychological	Bodily image and appearance	Spirituality/Religion/Personal beliefs
	Negative feelings	Thinking, learning, memory, and concentration
	Positive feelings	
	Self-esteem	
3. Social relationships	Personal relationships	Sexual activity
	Social support	
4. Environment	Financial resources	Opportunities for acquiring new information and skills
	Freedom, physical safety, and security	Participation in and opportunities for recreation/leisure activities
	Health and social care: accessibility and quality	
	Home environment	
	Physical environment	

to be the most common ADR while weight gain was the most common ADR found in the study conducted by Lucca et al. [14] After dividing the observed ADRs according to their systems for ease, EPS was found in 1% while weight gain in 7% of patients with ADRs. The drug responsible for the highest number of ADRs was olanzapine as an antipsychotic which is similar to the study accomplished by Lucca et al. [14] and venlafaxine as an antidepressant. APs were found to be responsible for a higher number of ADRs compared to ADs [Figure 4].

Causality assessment was done by WHO-UMC and Naranjo’s scale for the observed ADRs. The majority of ADRs could be classified as “Possible”

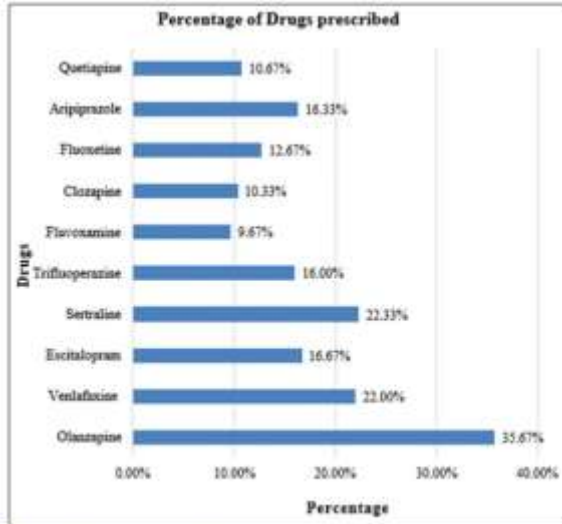


Figure 3: Percentage of drug prescribed

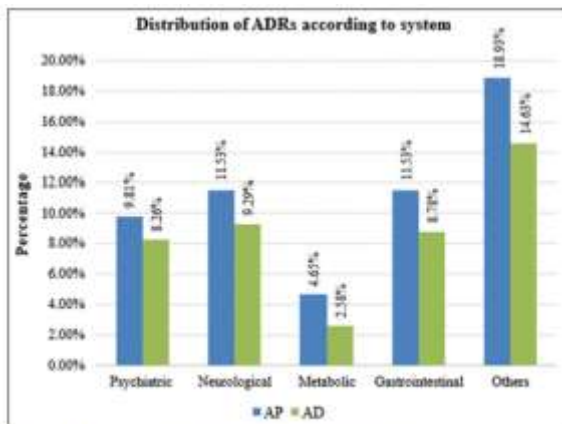


Figure 5: Distribution of ADRs according to system

at 65.48% (WHO-UMC causality assessment) and 90.65% (Naranjo’s causality assessment) in contrast to a study carried out by Shah et al. [24] in which the maximum ADRs were classified as “probable” followed by “possible.” No “certain” causes were seen since in cases where dechallenge was done, rechallenge was not attempted with the offending drug. This is following to study carried out by Munoli and Patil[26] Severity assessment was done by the Hartwig–Siegel scale. All the ADRs taken into

consideration for QOL were assessed for severity. Tremors and sensations in hands were classified to be mild. EPS, Parkinsonism, and seizures were classified into moderate severity similar to results achieved in the study concluded by Shah et al. [24] No cases of the fatal or life-threatening condition were encountered which is again following to study performed

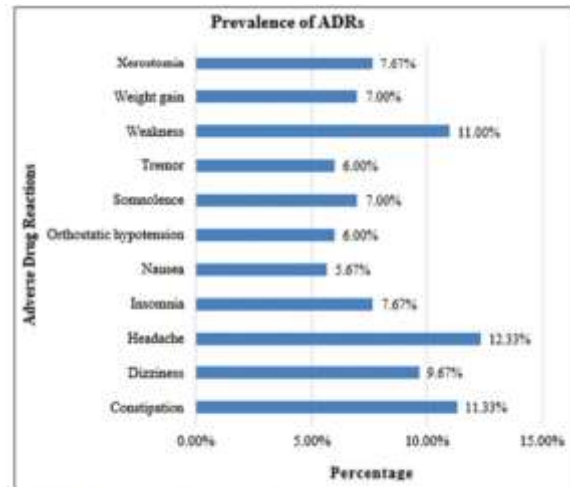


Figure 4: Prevalence of Majority of ADRs

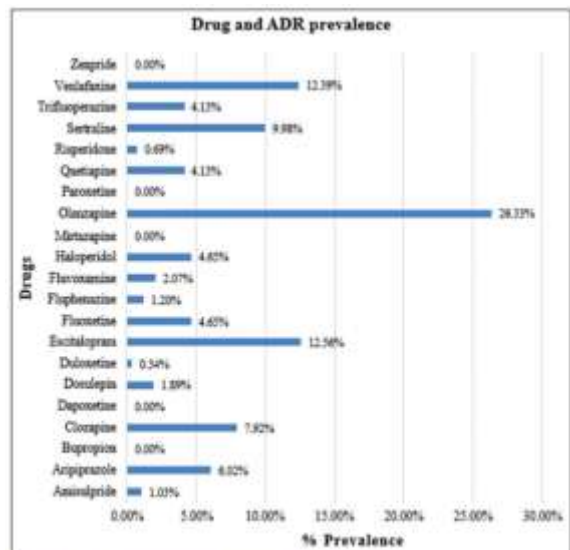


Figure 6: Drugs (AP/AD) and ADR Prevalence

by Shah et al. [24] Very few studies have been carried out to find the impact of ADRs due to psychotropic agents on the QOL of the patients. We carried out a QOL assessment of all the

major ADRs detected. Out of the four domains, physical, psychological, social, and environmental assessed, the QOL decreased significantly in the physical and psychological domains. The P values were also found to be significant, while the changes in the social and environmental domain are negligible. Their P value was also not significant. Even the study accomplished by Chawla and Kumar[18] showed a negative association of ADRs in the physical and psychological domain while the change in the

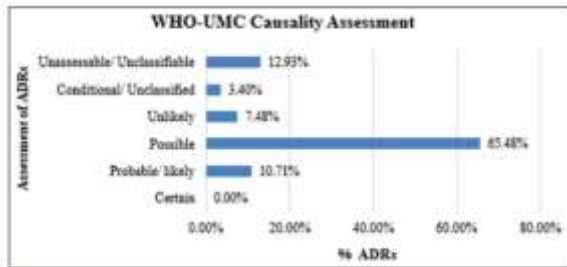


Figure 7: WHO-UMC Causality assessment of ADRs

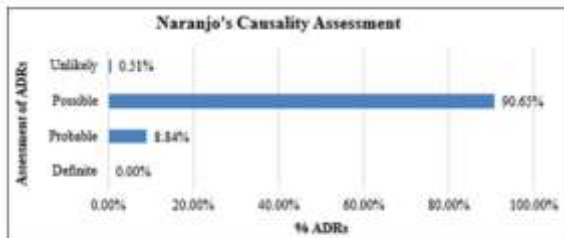


Figure 8: ADR Causality assessment as per Naranjo's Algorithm

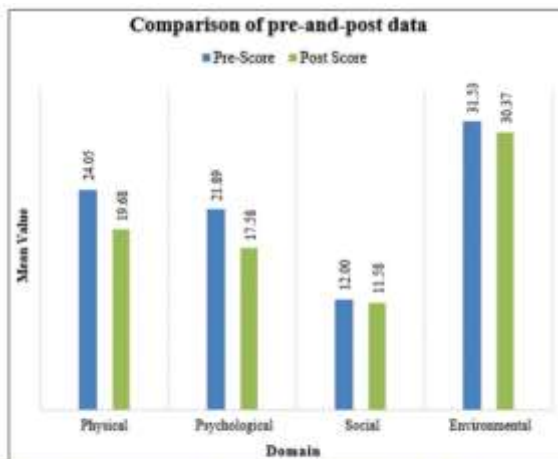


Figure 9: Comparison of Raw Score in WHO-BREF-QOL assessment

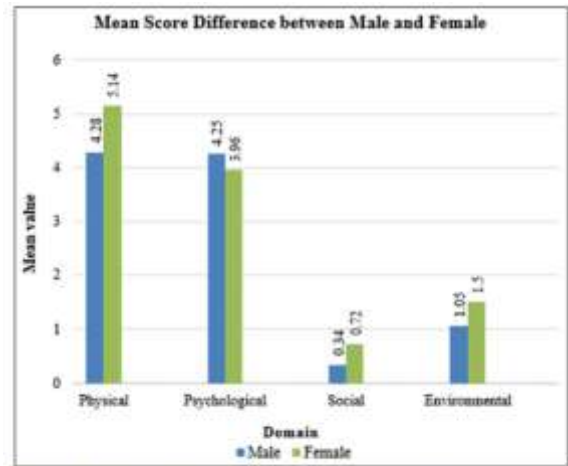


Figure 10: Mean difference of raw score biw male and female

social and psychological domain was not significant. The mean difference between the pre- and post-values of assessment in the physical domain showed more decrease in females than males which depicts that the changes in the physical domain have a higher impact on females, while in the psychological domain, the mean decrease was more in males than females which depicts that the changes in the psychological domain have a higher impact on males.

V. CONCLUSION

Owing to the increased use of psychiatric medications, this study is one of its kind to study prospectively the pattern of adverse drug reactions due to APs and ADs prescribed. As in this study, the overall prevalence of ADRs was found to be 24.33%, out of which olanzapine and escitalopram were responsible for maximum ADRs. Headache was the most prevalent ADR which cannot be considered as serious or severe. On the other hand, many moderately severe ADRs such as EPS, Parkinsonism, and seizures were also observed which need to be identified and managed on time. The need for PV is thus highlighted for early recognition, effective management, and a decrease in health-care costs to the patients. Intense monitoring of adverse drug reactions can help reduce their occurrence

by increasing awareness regarding their significance and reporting them to regulatory authorities. The major ADRs observed in this study showed a negative effect on the QOL of the psychiatric patients during the study period. Physical and psychological domains were affected significantly while changes in social and environmental domains showed no significance. Hence, not only the incidence, severity, and cost should always be considered while managing a patient but its impact on the QOL of the patient should also be prioritized. Further, multicenter studies focusing on long-term follow-up of all ADRs and their economic and QOL impact are needed to explore this area in much detail.

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