A Prospective Observational Study on Drug Utilization Pattern and Pharmacovigilance of Selective Serotonin Reuptake Inhibitors in a Tertiary Care Hospital

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Abstract

Background: Among the various psychiatric disorders, Major Depression Disorder (MDD) remains to be the leading cause of disability in the world. Since Selective Serotonin Reuptake Inhibitors(SSRIs) were the most commonly prescribed drug for MDD and various psychiatric illness, the objective of this study was to assess the drug utilization pattern and Adverse Drug Reactions(ADRs) associated with its usage.

Materials and Methods: This study was conducted in the psychiatry department of a tertiary care hospital for one year with sample size of 110 prescriptions. Collected data was entered in MS Excel and analyzed with SPSS version 26.

Results: Out of 110 patients, 46.4% were males and 53.6% were females. 21-40 years (49.1%) were the most commonly affected age group. Regarding the morbidity distribution pattern, depression disorder (75.5%) was the most commonly diagnosed psychiatric illness. Escitalopram was the most commonly prescribed SSRI. The average number of drugs per prescription was 2.07. Percentage of drugs prescribed in generic name was 30.7%. Percentage of drugs prescribed from Tamilnadu Essential Drug List(EDL) was 22.8%. Nausea, headache, insomnia and gastritis were the most commonly reported ADRs.

Conclusion: We conclude that escitalopram with clonazepam as Fixed Dose Combination (FDC) was the preferred regimen because of their better efficacy, safety and tolerability over other antidepressants (ADs). The prescription pattern of SSRIs was almost appropriate. Certain factors like prescribing in generic name, dispensing drugs from hospital drug store at free of cost and adding up of more drugs to State's EDL should be instigated to abate economic burden and to improve patients adherence to therapy.

Keywords: Defined Daily Dose (DDD), Drug Utilization Study (DUS), International Network for Rational Use of Drugs (INRUD), Major Depression Disorder (MDD), Prescribed Daily Dose (PDD), Selective Serotonin Reuptake Inhibitors (SSRIs)

Introduction

Psychiatric disorders forms an important health concern, which manifests either as a primary disorder or as a co-morbid condition. Mental disorders burden had enormously risen over the last few decades. WHO (World Health Organization) estimated that globally, over 450 million people suffer from mental disorders and currently, mental and behavioural disorders account for about 15 percent of the global burden of diseases. This is likely to increase to 25 percent by 2025[1]. The COVID-19 pandemic has

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affected the mental health (e.g., depression, anxiety, sleep disorders, and posttraumatic stress symptoms) of children and adolescents[2]. Depression is widely recognized as a major public health problem around the world among the psychiatric disorders. The COVID-19 pandemic has undoubtedly doubled the risk of depression[3]. By 2030, unipolar depression is predicted to be the second leading contributor to the global burden of disease[4]. To treat depression disorder, Antidepressants (ADs) are widely prescribed. Choosing a suitable antidepressant for a particular patient depends on many factors like patient's demographic profile, comorbidities, side effects of the drugs and cost effectiveness.

In the last decade, there had been a gradual shift in the prescribing trends of antidepressants from tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAO inhibitors) towards Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitor (SNRIs)[5]. Since so many drugs are available in this group with much diversity, it is prudent to analyse the drug utilization pattern of SSRIs. Apart from MDD, these SSRIs are also widely used in the pharmacotherapy of wide range of psychiatric disorders including Obsessive compulsive disorder(OCD), Adjustment Disorder, Anxiety Disorder, Social Phobia, Premenstrual dysphoric disorder(PMDD), Post traumatic stress disorder(PTSD) and Eating disorder irrespective of existence of co-morbid depression in these situations[6,7].

Drug utilization research(DUR) was stated by WHO as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences"[8]. As there was an increase in diversity of the diseases, corresponding usage of drugs had also increased. In such a situation, physicians were expected to prescribe the drugs rationally to every patient. On the contrary, the scenario was completely different because irrational prescribing was becoming a global issue[9]. The principle aim of drug utilization study was to nurture the habit of rational use of medicine. This was quoted by WHO (1985) as "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and

their community". Defined Daily Dose (DDD) was the assumed average maintenance dose per day for a drug used for its main indication in adult. It was just a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose (PDD). PDD was defined as the average dose prescribed according to a representative sample of prescriptions.

Pharmacovigilance(PV) was defined as "the pharmacological science relating to the recognition, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines[10]. PV includes monitoring ADRs associated with allopathic products, herbal products, traditional complimentary medicines, blood products, vaccines, biologicals and medical devices.

DUS is an inexpensive tool for the evaluation of current prescribing patterns. Therefore this kind of studies were useful to achieve rational and cost effective therapeutic practices in healthcare. This study was conducted to assess prescription pattern as per WHO/INRUD, to delineate the therapeutic uses SSRIs in various psychiatric disorders and documenting adverse drug reactions reported by the patient during follow up period.

Though there were many drug utilization data of antidepressants, the purpose of our study was to contemplate the drug use pattern of SSRIs exclusively.

Materials & Methods:

Study Design: The present study was a prospective, observational study to evaluate the drug utilization pattern of SSRIs and ADRs encountered during the follow up period.

Study Setting: This study was conducted in the psychiatry out patient department(OPD) of Rajah Muthiah Medical College and Hospital (RMMCH), a tertiary care teaching hospital under Annamalai University, Chidambaram, Tamilnadu, India.

Study Period: Study was carried out for period of one year from July 2021 to June 2022

Sample Size: 110 prescriptions were analysed.

Study Participants:

Inclusion Criteria:

Patients attending psychiatry OPD, RMMCH with their prescription having atleast one SSRIs irrespective of their age, sex, comorbities etc. These patients were thoroughly examined and assessed about the duration of disease, treatment, relapse, compliance and were followed up. Adverse drug reactions occured during follow up therapy were also noted.

Exclusion Criteria:

Patients who were not willing to participate in the study. Patients with severe psychiatric and physical illness who could not co-operate with the study.

Study Procedure:

The proposal for this DUS was submitted to the Institutional Human Ethics Committee(IHEC), and approval was obtained before commencing the study (IHEC/764/2021). The data was obtained from patients attending psychiatry OPD during the period July 2021 - June 2022. The data were collected using a pre-designed pro forma. The individual participants were explained about the nature of the study in their own language and they were assured that their identity would be kept confidential and that they could refuse to participate in the study at any point of time. Written and informed consent was obtained from the participants in both English and Tamil.

Data Collection:

Demographic details like name, age, gender, OP/IP number and socio-economic status. Prescription details such as clinical diagnosis, name of the individual drug, dosage form and dosage schedule. During follow up period (revisit), information regarding adherence to therapy, improvement of symptoms and adverse effects if any, were noted.

Data Analysis:

Analysis of prescribing indicators using WHO/INRUD drug use indicators. Classification of prescribed drugs as per Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose(DDD) classification system. The PDD and its ratio to DDD was calculated. The cross tabulation and Pearson Chi square test were used to find out association between the diagnosis and the drug used. Data collected was entered in MS Excel and was analyzed with SPSS version 26.

Results

Demographic Data Analysis:

Age Wise Morbidity Distribution Pattern: Among the study population, majority of the patients (49.1%) fell under the age group of 21-40 years as shown in Table 1. Morbidity distribution pattern of psychiatric illness were shown in Figure 1.

Table 1. Age wise morbidity distribution pattern

Diagnosis	Age Group(in years)								
	<20		21-40		41-60		>60		
	n	%	n	%	n	%	n	%	
Depression Disorder	3	75	36	66.7	35	85.4	9	81.8	Chi square value - 10.784 & p-value - 0.768
Anxiety Disorder	1	25	8	14.8	3	7.3	-	-	
Obsessive Compulsive Disorder	-	-	2	3.7	-	-	-	-	
Adjustment Disorder	-	-	4	7.4	1	2.4	1	9.1	
Phobia	-	-	2	3.7	2	4.9	1	9.1	
Schizophrenia	-	-	2	3.7	-	-	-	-	
Total Patients (n=110)	4 (3.6%)	100	54 (49.1%)	100	41 (37.3%)	100	11 (10%)	100	

Figure 1. Morbidity Distribution Pattern of All Psychiatric Illness
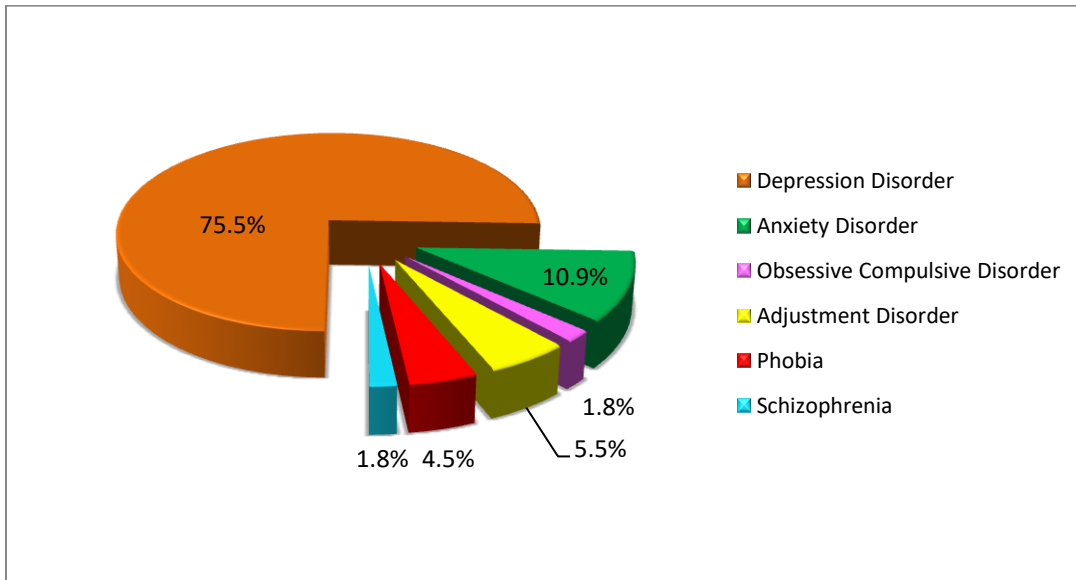

Gender wise Morbidity Distribution Pattern: On comparison of the study population from Table 2, the prevalence of psychiatric illness was more among females (53.6%) than males (46.4%) and the most common psychiatric illness was depression disorder in both gender.

Table 2: Gender wise morbidity distribution pattern

Diagnosis	Gender				
	Male		Female		
	n	%	n	%	
Depression Disorder	35	68.62	48	81.35	Chi square value-9.304 & p-value-0.098
Anxiety Disorder	8	15.70	4	6.77	
Obsessive Compulsive Disorder	2	3.92	-	-	
Adjustment Disorder	1	1.96	5	8.50	
Phobia	4	7.84	1	1.69	
Schizophrenia	1	1.96	1	1.69	
Total Patients (n=110)	51 (46.4%)	100	59 (53.6%)	100	

Socioeconomic status according to occupation: On analysis of patients socioeconomic status according to their occupation, majority of study population with psychiatric condition were house wives(32.72%) as shown in Figure 2.

**Figure 2: Socioeconomic status according to occupation**
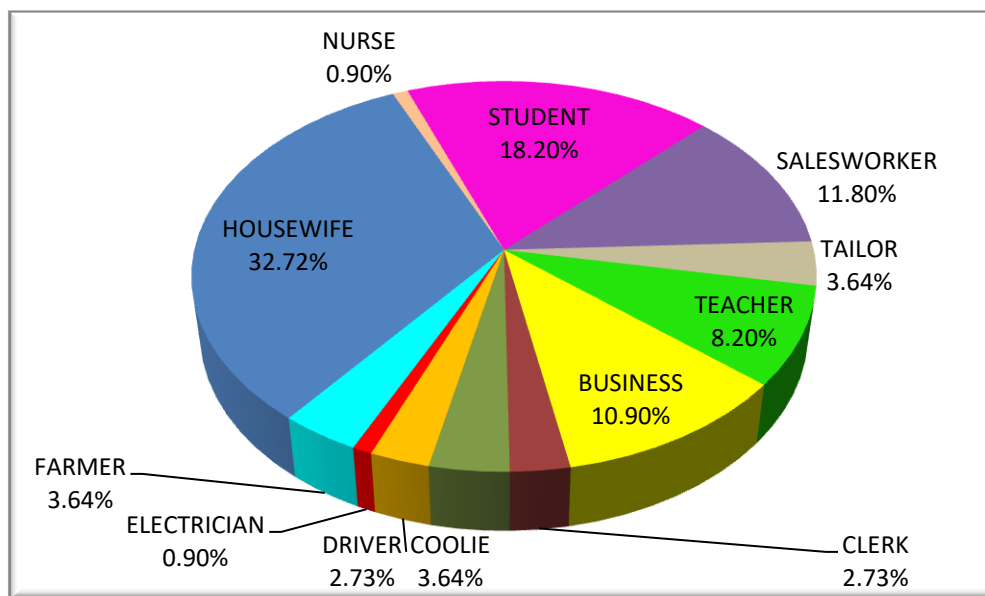
Prescription pattern of SSRIs: In our study, escitalopram was the most commonly prescribed SSRI followed by fluoxetine and sertraline which were used in very few conditions only. Escitalopram with clonazepam as Fixed Dose Combination(FDC) was the most commonly prescribed drug as depicted in Table 3 and Figure 3.

Table 3: Prescription pattern Of SSRI

SSRI Prescription Pattern	Depression Disorder		Anxiety Disorder		Obsessive Compulsive Disorder		Adjustment Disorder		Phobia		Schizophrenia		Total Prescription Pattern (n=110)	
	n	%	n	%	n	%	n	%	n	%	n	%		
Escitalopram with Clonazepam	49	59.1	8	66.7	-	-	4	66.7	3	60	-	-	64 (58.2%)	Chi square value-45.601 & p-value-0.001
Escitalopram	30	36.1	4	33.3	-	-	2	33.3	2	40	1	50	39 (35.5%)	
Fluoxetine	3	3.6	-	-	2	100	-	-	-	-	1	50	6 (5.4%)	
Sertraline	1	1.2	-	-	-	-	-	-	-	-	-	-	1 (0.9%)	
Total Psychiatric Illnes (n=110)	83 (75.5%)	100	12 (10.9%)	100	2 (1.8%)	100	6 (5.5%)	100	5 (4.5%)	100	2 (1.8%)	100	110 (100%)	

Figure 3: Morbidity wise prescription pattern of SSRI
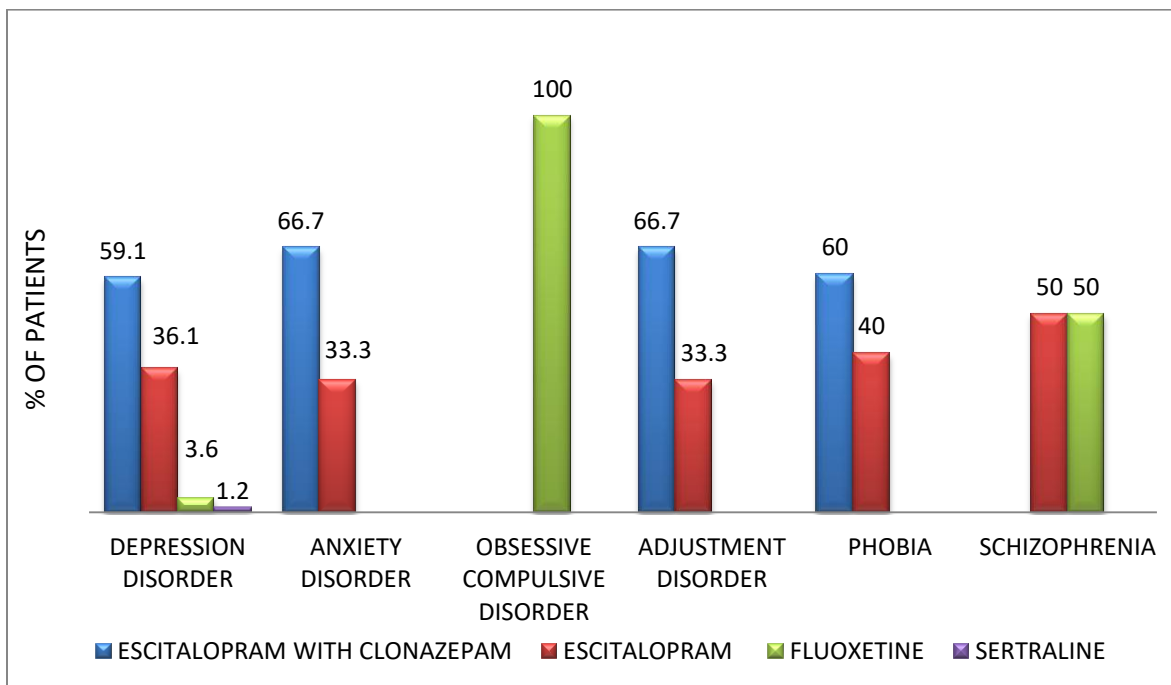
Assessment of prescription pattern as per WHO/INRUD drug use indicators:

The prescribed drugs were analyzed as per WHO/INRUD prescribing indicators and the results obtained were depicted in Table 4.

Table 4: Prescription pattern analyzed as per WHO/INRUD drug use indicators

Drug use core indicators	Values
Average number of drugs per prescription	2.07
Percentage of drugs prescribed by generic name	30.7%
Percentage of prescriptions containing FDC	58%
Percentage of drugs prescribed from Tamilnadu essential drugs list	22.8%
Percentage of SSRI prescribed from Tamilnadu essential drugs list	3%
Percentage of SSRI purchased by patient from external sources	100%
Percentage of drugs dispensed from hospital drug store at free of cost	16.2%

ATC/DDD classification of prescribed drugs:

In our study, all the drugs prescribed were coded by ATC classification. On comparing prescriptions, there were multiple doses of each drug. So the average of daily doses was taken as PDD. Finally, PDD-to-DDD ratio was calculated, as shown in Table 5.

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Table 5. ATC/DDD drugs classification

| Drug	ATC code	PDD(mg)	DDD(mg)	PDD/DDD
Escitalopram	N06AB10	8.861	10	0.886
Fluoxetine	N06AB03	20	20	1
Sertraline	N06AB06	50	50	1
Clonazepam	N03AE01	0.527	8	0.065
Diazepam	N05BA01	5	10	0.5
Lorazepam	N05BA06	1.4	2.5	0.56
Amitriptyline	N06AA09	25	75	0.333
Zolpidem	N05CF02	10	10	1
Duloxetine	N06AX21	20	60	0.333
Mirtazapine	N06AX11	10	30	0.333
Quetiapine	N05AH04	50	40	1.25
Risperidone	N05AX08	2	5	0.4
Olanzapine	N05AH03	2.5	10	0.25
Amisulpride	N05AL05	200	400	0.5
Propranolol	C07AA05	20	160	0.125

Pharmacovigilance:

The patients under study were scheduled for follow up once in 15 or 30 days, to receive a new prescription and during their follow up, they were enquired for any ADRs. Out of 110 patients, 88 patients (80.2%) did not report any side effects, remaining 22 patients (19.8%) had reported adverse effects as shown in Table 6 & Figure 4.

Table 6. ADRs encountered during follow up of patients

Adverse effects	No of patients (n=110)	Percentage
No ADR	88	80.2
Nausea	3	2.7
Headache	3	2.7
Insomnia	3	2.7
Gastritis	3	2.7
Weight Gain	3	2.7
Headache with Dryness of mouth	1	0.9
Headache with Insomnia	1	0.9

Headache with Diarrhoea	1	0.9
Insomnia with Nausea	1	0.9
Diarrhoea	1	0.9
Dark coloured stools	1	0.9
Dark coloured stools with Nausea	1	0.9

Figure 4. ADRs encountered during follow up of patients
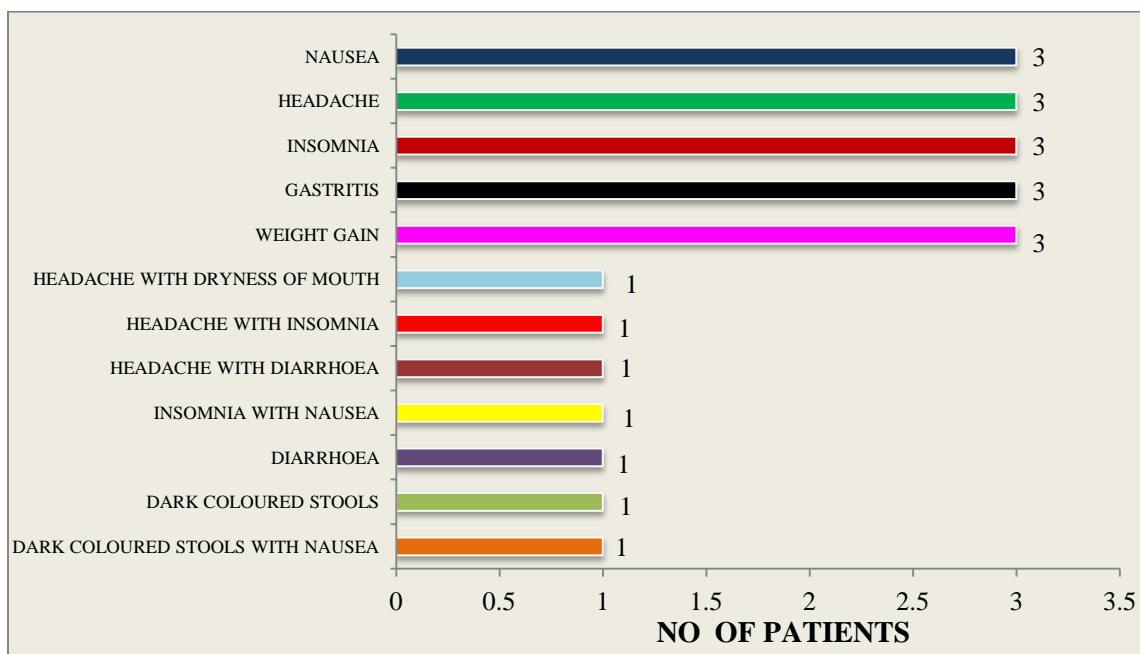
Discussion

Figure 1 shows the morbidity distribution pattern of all psychiatric illness, in which 83 patients were diagnosed to have Depression disorder (75.5%), followed by 12 patients with anxiety disorder (10.9%). Six patients had adjustment disorder (5.5%), 5 patients had phobia (4.5%) and 2 patients had both obsessive compulsive disorder and schizophrenia(1.8%). This finding was supported by another prospective observational drug utilization study[11], where depression disorder showed maximum prevalence around 42.88% and many other studies also[12-14]. A Systematic Review and Meta-Analysis study by Cenat et al[15], revealed that there was increased prevalence of psychological distress in people during COVID-19 pandemic and ended up in facing serious psychiatric and neuropsychiatric

problems (such as depression, impaired memory, insomnia and sleep disorders, anxiety, and PTSD, etc.)

As shown in Table 1, age wise morbidity distribution pattern was done. Majority of the patients (49.1%) fell under the age group of 21-40 years. In that category, 66.7% (36 numbers) had depression disorder, followed by anxiety disorder which was around 14.8% (8 numbers), then 7.4% (4 numbers) had adjustment disorder. And 3.7% (2 numbers) had OCD, phobia and schizophrenia. Next to adolescent age group, 37.3% (41 numbers) of the total study group was categorized under 41-60 years. In that category also, majority of patients ie around 85.4% (35 numbers) had depression disorder, followed by anxiety disorder (7.3%, 3 numbers). 4.9% (2 numbers) had phobia and 2.4% (one number) had

adjustment disorder. 11 patients (10%) belonged to geriatric population (>60 years) in the present study. Among them, depression disorder was the most prevalent condition (81.8%) and 9 patients were suffering by this condition, followed by adjustment disorder and phobia which was around 9.1% (one number) each. Finally only 3.6% (4 numbers) of study population fell under less than 20 years age category in which 3 patients(75%) had depression disorder and one patient (25%) had anxiety disorder. In a psychotropic drug utilization study[16], most of the patients (50.6%) were in the age group 21-40 years, which correlates with our study finding and also with similar other studies[17,18]. Stressful life events, increased exposure to social media, extended home confinement, brutal grief, intra familial violence, were the factors contributing to increased mental health disorders among adolescents age group. COVID-19 pandemic added up fuel to fire and adolescents were the vulnerable population for mental health disorders and they require careful consideration by family members and health care system[19].

On comparison of the study population (from Table 2), the prevalence of psychiatric illness was more among females (53.6%) than males (46.4%) and the most common psychiatric illness was depression disorder in both gender. Biological changes and hormonal fluctuations during puberty, prior to menstruation, following pregnancy and at perimenopause were the reason behind higher incidence rate of depression among women. In the factors influencing depression endpoints research study, FINDER study[20], females (68.2%) outnumbered the males, which is in concordance with our finding. Gender distribution of anxiety disorder showed higher preponderance in males than females[21], and this finding parallels with our study results.

On analysis of patients according to their occupation as shown in Figure 2, majority of study population were house wives (32.72%) and it was supported by similar other study[22] which revealed the reason for higher rates of mental disorders in among housewives result from their lack of appreciation within society and from weariness due to workload at home. Next to housewives, students population showed increased prevalence around 18.20%. Several national surveys of college counseling directors indicated that the prevalence and severity of significant mental health problems were increasing in the college student population[23]. It was then followed by sales worker (11.80%), business group (10.90%), teacher (8.20%). Coolie, farmer and tailor occupations showed equal distribution (3.64%), likewise clerks and driver took up 2.73% of study population each. Finally nurse and electrician occupied the least amount i.e., 0.90% each.

Out of 110 prescriptions, prescription pattern of SSRI(Table 3 & Figure 3) showed that in depression disorder, 59.1% (49 numbers) received escitalopram with clonazepam, 36.1% (30 numbers) received escitalopram, 3.6% (3 numbers) received fluoxetine and 1.2% (one number) received sertraline. In the both anxiety and adjustment disorder, 66.7% received escitalopram with clonazepam and 33.3% received escitalopram. Among OCD, all patients received fluoxetine. In phobia, 60% (3 numbers) received escitalopram with clonazepam and 40% (2 numbers) received escitalopram and lastly in schizophrenia, both escitalopram and fluoxetine was prescribed in equal percentage. In our study, escitalopram was the most commonly prescribed SSRI followed by fluoxetine and sertraline. Various other studies have also strongly supported our finding[24-27]. The SSRI usage trend has increased exponentially over years[28], this might be because of their increased efficacy, wide therapeutic uses and better knowledge about their adverse effects on comparison to first generation antidepressants like TCA, MAO inhibitors. Escitalopram was most commonly prescribed as FDC with clonazepam . The rationale behind addition of benzodiazepine with SSRI lies in the fact that it achieves rapid symptom relief at the beginning of therapy, until SSRI begins to exert its effect, reduces SSRI induced agitation in the early course of therapy and finally improves adherence to SSRI medication, which may ultimately improve overall outcomes[29]. The long half-life and higher potency of clonazepam may allow easier discontinuation with fewer withdrawal symptoms compared to other benzodiazepines[30].

For rational use of drugs, WHO has developed core prescribing indicators which includes prescribing indicators, patient care indicators and health facility indicators. In our study, all the prescribed drug were analyzed as per WHO/INRUD drug use indicators as

shown in Table 4. Out of 110 prescriptions, a total of 228 drugs were prescribed. And the average number of drugs per prescription were 2.07 with a maximum of five drugs, which is within the acceptable range compared with the standard (1.6-1.8) values[31]. Our observation was also similar to other studies[16,32]. Hence polypharmacy was avoided in our study and no patients had prescriptions containing more than five drugs. On the other hand, only 30.7% of drugs were prescribed in generic name, which was very low when compared with WHO standard value of 100%. And this was also similar to other studies, where 25.37%[33] and 29.27%[34] of drugs were prescribed in generic name. The Ministry of India has also issued orders to MCI, all state and central government hospitals to ensure the prescription of drugs in generic name[35]. Hence we should encourage generic prescribing in our setting. Percentage of prescriptions containing FDC were 58%. The only FDC used in our study was escitalopram with clonazepam. Percentage of drugs prescribed from Tamilnadu EDL was 22.8%, which had also failed to meet the optimal value of 80-100%. Several other studies[36,37] on drug prescribing indicators also documented a meagre prescription from essential drug list. Finally, only 16.2% of total drugs was dispensed from hospital pharmacy at free of cost and remaining 83.8% was purchased from other outlet at their own cost. All the SSRIs prescribed in this study was purchased by patients in outside pharmacies, and the average cost per prescription was around INR 100-150/-, which correlates with other study[38]. This high cost was because of prescription of drugs in brand names. This again highlighted the need to prescribe generic drugs and to choose brands that offer good quality, low cost drugs.

In our study, the total consumption of drugs was analysed according to WHO ATC/DDD classification system. PDD/DDD ratio determines whether the drug was underutilized (<1) or overutilized (>1). PDD can vary according to both the illness treated and national therapeutic traditions. As shown in Table 5, The PDD/DDD ratio was equal to one for fluoxetine, sertraline and zolpidem. This ratio was highest for quetiapine (1.25). For all the remaining drugs, it was found out to be less than one.

Out of 110 patients(from Table 6 & Figure 4), 88 patients(80.2%) did not report any side effects,

remaining 22 of them (19.8%) had reported adverse effects. Females experienced a higher incidence of ADRs (13 numbers, 59%) than males (9 numbers, 41%). The majority of the patients (13 numbers, 59%) were in the age group of 20-40 years. In those 22 patients, 3 patients in equal percentage of 2.7% each had nausea, headache, insomnia, gastritis and weight gain. Headache with dryness of mouth, headache with insomnia, headache with diarrhoea, insomnia with nausea, diarrhoea, dark coloured stools and dark coloured stools with nausea were reported in equal percentage (0.9% each). Nausea, diarrhoea, headache, insomnia and gastritis were frequent ADRs with SSRI (mainly escitalopram), which correlates with the study done by Sankhi et al[39]. Weight gain was because of atypical antipsychotics like olanzapine and quetiapine. Finally dry mouth was reported by patient taking TCA(Amitriptyline). When ADR was observed according to prescription pattern of SSRI, patients who received escitalopram in combination with clonazepam reported relatively less ADRs than who received plain escitalopram. There was no history of suicidal thoughts among patients.

Though we have meticulously conducted our study, there were several limitations. Our study results would have been much more precise and validated with a larger sample size. We would have got more information regarding efficacy and safety of the prescribed SSRIs, had we followed it up for a longer duration.

Conclusion

In recent years, DUS has become a popular tool used in the evaluation of health care system for rationale use of medicine. And this study was a sincere attempt to analyze the drug utilization pattern of SSRIs and their ADRs. We have found out that SSRIs were the most commonly prescribed antidepressants because of their better efficacy, safety, tolerability and fewer adverse effects. Among SSRIs, escitalopram was the most commonly prescribed drug. In our study, most of the prescriptions were prescribed according to WHO/INRUD drug use indicators. Still we need to encourage the habit of prescribing in generic name and adding up more drugs to the State's EDL to increase patients compliance and a long term follow up also needs to be done.

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