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Original Research Article

Drug utilization study of off-label drug use in outpatient department of psychiatry: a prospective study at a tertiary care teaching hospital

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ABSTRACT

Background: In the absence of standard psychiatric prescribing information, physician often use drugs in an off-label way. Many studies have been published across the globe reporting different rates of off-label use. There is currently no study based on Indian Drug Formulary.

Methods: After taking permission from Institutional Ethics Committee (IEC), a prospective study was conducted among 285 patients attending Psychiatry outpatient department for the period of 4 months. Data related to demographic parameters, diagnosis of psychiatry conditions and drugs details were collected directly from the patient's medical records and entered in Case Record Form (CRF).The off-label drugs were categorized as per National Formulary of India. Multivariate binary logistic regression model was used to determine the predictors of off- label drug prescribing. The data were statistically analyzed using SPSS version 19 and chi-square test.

Results: A total of 285 patients (169 males, 116 females) were included in the study with mean age of 36.54 ± 13.91 years. Most of the patients (n=65, 22.8%) were diagnosed as schizophrenic. Out of 285 patients, 133(46.6%) received at least one off-label drug. A total 841 drugs were prescribed out of which 167(19.85%) were off-label. The drug most frequently prescribed as off-label were trihexiphenidyl HCL 29 (10.2%), clozapine 23 (8.1%) and clonazepam 13 (4.6%).

Conclusions: Off label drugs used among psychiatry patients was 19.85%. The most frequently used off-label drugs was trihexiphenidyl HCL. The use of off-label drugs in psychiatric patients has been reportedly increasing which warrant national drug regulatory authorities to review and revise safe administration such drugs.

Keywords: Label drug, Psychiatry, Prescription, Outpatients, Off-label drug

INTRODUCTION

All medications are good and beneficial in treating disease, but it's important to understand what medications are intended for and how to use them appropriately The label drugs means they are approved by Food and Drug Administration (FDA) only for a specific indication.[1] Drugs have to undergo rigorous scrutiny before marketing approval in the form of in vitro studies, animal studies and clinical trials. These data provide labeling information like approved indications,

appropriate dosing and the specific populations for its use.[2,3]

Off-label drug use refers to the use of drug by a physician outside of its approved age, diagnosis, dose, frequency, duration, route and contraindication for its administration. Off-label drug is not illegal provided the judgment is based on scientific evidence that has been accepted by professional bodies and is commonly seen in the fields of pediatrics, oncology and psychiatry.[4-6]

The prescription of psychotropic drugs for management of psychiatric conditions across all age groups is rising worldwide.[7-10] Evidence showed that some antipsychotics are frequently prescribed as off-label for unapproved indication but only 4% of cases were supported by powerful clinical evidence.[9] Whereas, in India only two studies reported that the prevalence of prescribing off label drugs were 39.5% and 42.34% as per British National Formulary.[11,12] Through extensive literature review it was revealed that till date no such study is conducted in India as per National Formulary of India (NFI). Hence, aim of this study was to evaluate the use of off-label drugs as per National Formulary of India (NFI) - 2016, 5th edition and also to identify various predictors for off- label drug prescribing.[13]

METHODS

Data collection

A prospective study was conducted among 285 psychiatric patient attending outpatients Department at Gujarat Medical Education Research Society (GMERS) medical college, Patan, Gujarat. The study was conducted for 4 months from August 2016 to December 2016. Before conducting the study approval was obtained from Institutional Ethics Committee, GMERS, Patan, Gujarat. All the patients attending the psychiatric outpatient department were included in the study. The purpose of the study was explained to the patients and the inform consent was obtained from those who are willing to participate in the study.

Data related to demographic parameters (age, gender), diagnosis of psychiatry conditions and drugs details (dose, route, frequency and duration of administration.) were collected directly from the patient's medical records. Off-label prescribing was assessed for indication, dose, duration and dosage form as per NFI [13]approved indications.

Statistical analyses

The data were analyzed by using SPSS version 19.0 IBM Corporation. Chi-square test was used to determine the significant difference between the proportions of label and off-label prescribing for different variables. Multivariate binary logistic regression model was used to control the multiple predictors for off-label prescribing.

The predictors variable considered for the enter step of the logistic regression analysis were demographics (age, gender), psychiatry disorder and other co-morbidities. $P<0.05$ was considered as statistically significant.

RESULTS

Demographic characteristic

A total 285 patients were included in the study with a mean age of 36.54±13.91 years. Out of 285 patients 169 (59.3%) were male and 116 (40.7%) female.

Disease characteristic

Majority of the patients diagnosed were schizophrenic 65 (22.8%) followed by depression 30 (10.5%), generalized anxiety 22 (7.7%), bipolar affective disorder 22 (7.7%), mania 19 (6.7%) and obsessive compulsive disorder 15 (5.3%). Other morbidities like alcohol dependence, posttraumatic stress disorder (PTSD) and mild mental retardation comprise of 29 (10.18%). Co-morbidities like seizure 45 (15.8%) other conditions like migraine and headache 29 (10.2%) were also included.

Characteristic of label and off-label drug prescribing

Out of 841 drugs prescribed, 674 (80.1%) were label drugs. Figure 1 shows the distribution of label drug prescription among the psychiatry patients. The most commonly prescribed label drugs were lorazepam 90 (31.6%), olanzepine 69 (24.2%), trihexiphenidyl HCL 60 (21.1%), imipramine 52 (18.2%) and clonazepam 49 (17.2%).
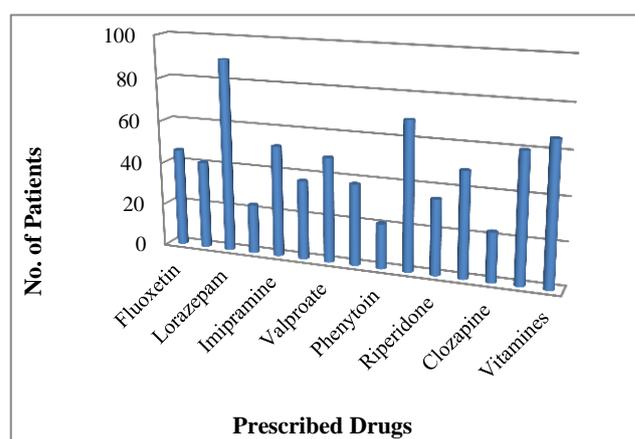

Figure 1: The distribution of label drug prescription among the psychiatry patients.

Out of 841 drugs prescribed, 167 (19.9%) were off label drugs. Figure 2 shows the distribution of off-label drug prescription among the psychiatry patients. The most commonly prescribed in off-label drug were trihexiphenidyl HCL 29 (10.2%), clozapine 23 (8.1%), clonazepam and sodium valproate 13 (4.6%) each.
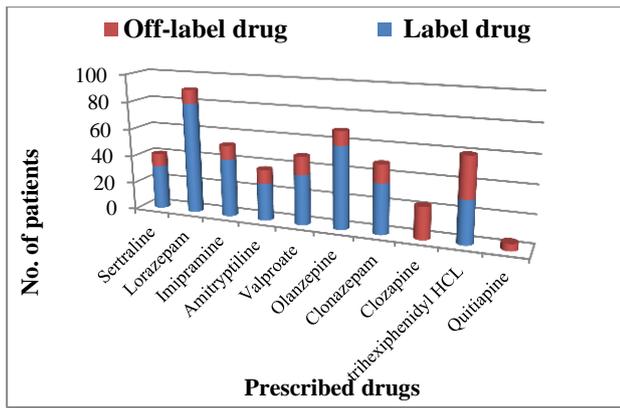
Figure 2: The distribution of label and off-label drug prescription among the psychiatry patients.

Table 1: Distribution of label and off label drugs according to demographic and clinical characteristics among Psychiatric patients.

Variables	Number of patients	Number of label	Number of off - label	P Value
Gender				
Male	169	85	84	0.22[b]
Female	116	67	49	
Age groups (in years)				
1-20	40	21	19	
21-40	141	75	66	0.36[a]
41-60	91	46	45	
61-80	13	10	03	
Morbidities				
Schizophrenia	65	28	37	0.05[b]*
No schizophrenia	220	124	96	
MDD	30	16	14	0.99[b]
No MDD	255	136	119	
BPD	22	12	10	0.91[b]
No BPD	263	140	123	
Mania	19	8	11	0.31[b]
No Mania	266	144	122	
OCD	15	9	6	0.59[b]
No OCD	270	143	127	
GAD	22	11	11	0.74[b]
No GAD	263	141	122	
Others	29	17	12	0.54[b]
No Others	256	135	121	
Co-morbidities				
Epilepsy	45	25	20	0.74[b]
no epilepsy	240	127	113	
Others	38	26	12	0.04[b]*
no others	247	126	121	

[a]Chi-square test, [b]Chi-square test with continuity correction, *Significant at P<0.05; MDD- Major Depressive disorder, BPD- Bipolar disorder, OCD- Obsessive compulsive disorder, GAD-Generalized anxiety disorder

Table 1 shows the distribution of label and off label drugs according to demographic and clinical characteristics among the psychiatry patients.

There was a statistical significant difference when the proportion of both drugs was compared for schizophrenic patients (P ≤0.05) and for other co-morbidity (P≤0.04). Out of 285 patients, 133 (46.6%) of patients received off-label drugs according to NFI. Off–label prescribing was more common among patients ranging between 21-40 age group 83 (49.7%). Off-label use was more frequent in patients with schizophrenia 53 (31.7%) followed by depression 15 (9%), both in bipolar disorder and generalized anxiety 22 (7.7%).

Multivariate binary logistic regression analysis was done for predicting off-label prescribing. None of the predictors (age, gender, psychiatric disorder and others comorbities) shows statistically significant difference Table 2.

Table 2: Predictors for off-label prescribing in the psychiatry outpatients department.

Variables	β coefficients	OR	95% CI	P value
Age groups (in years)				
0-20	1.16	3.19	0.68-15.1	0.14
21-40	1.07	2.91	0.69-12.3	0.15
41-60	1.29	3.65	0.86-15.6	0.08
Gender (male)	0.37	1.45	0.88-2.39	0.15
Morbidities				
Schizophrenia	-0.16	0.85	0.09-7.72	0.89
BPD	-0.71	0.49	0.05-4.95	0.55
Mania	-0.16	0.85	0.08-8.83	0.89
GAD	-0.53	0.59	0.06-5.64	0.65
OCD	-0.89	0.41	0.04-4.46	0.46
Others	-0.95	0.39	0.04-3.83	0.42
Co morbidities				
Epilepsy	-0.65	0.52	0.06-4.82	0.57
Others	-1.17	0.31	0.03-2.91	0.31
Constant	-0.89	0.41	-	0.43

OR: Odd ratio, CI: Confidence interval
Major Depressive disorder, BPD- Bipolar disorder, OCD- Obsessive compulsive disorder, GAD-Generalized anxiety disorder

Figure 3 shows the distribution of label and off-label drug according to psychiatry disorder. The most common off-label drug prescribing was for diagnosis of schizophrenia 53 (31.7%) followed by depression 15 (9.0%), generalized anxiety 15(9.0%) and bipolar disorder and mania same 12 (7.2%).
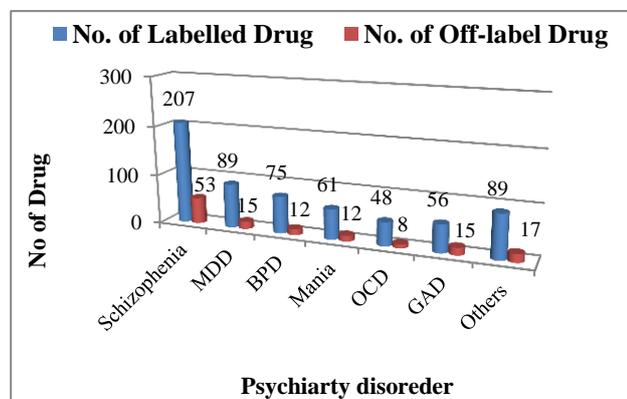

Figure 3: The distribution of label and off-label drugs according to psychiatry disorder.

DISCUSSION

The aim of our study was to evaluate the proportion of off-label prescribing based on NFI in psychiatric outpatients department. Mean age of patients in our study was 36.54 years which was slight higher than previous studies conducted by Jacob MK et al (34.59 years) and Thakker KB et al (33.9 years).[12,14] This slight difference might be due to geographical variation. Male subjects were slightly dominating with a proportion of 1.2:1 which was similar to previous studies.[12,14,15]

In the present study most common psychiatry disorder was diagnosed as schizophrenia followed by depression and bipolar disorder which was in accordance with previous studies.[12,15] We found a significant result in schizophrenia and other comorbidities of psychiatry patients but not seen in previous study.[11]

In our present study, the proportion of prescribing off label drugs was 19.85%. This was lower compared to previous studies conducted by Kharadi et al and Jacob et al showing proportion of 39.5% and 46.41% respectively.[11,12]

The major off-label drug used was trihexyphenidyl HCL, which act as centrally-acting anticholinergic drug mainly indicated for bipolar disorder, obsessive compulsive disorder, and schizophrenia. The reason for prescribing trihexyphenidyl HCL is to decrease the incidence of extra-pyramidal reactions to anti-psychotic drug as a prophylactic measure.[17]

The second off-label drug prescribed was from benzodiazepine group (9.5%). This was lower as compared to previous studies conducted by Kharadi et al and Jacob et al showing proportion of 24.5% and 35.29% respectively.[11,12] Benzodiazepines have been considered as the treatment of choice for catatonia.[18] Nowadays, benzodiazepines have been used as off-label drug in depression.[14] It is also effective in psychiatry disorders like insomnia, anxiety, panic disorder and alcohol withdrawal syndrome.[15] Lorazepam is the most commonly prescribed in long stay wards, typically for anxiety, aggression and agitation, while clonazepam is used in mania, anti convulsive effect in subclinical epilepsy and for anti anxiety effect.[15,16,19] Curtin suggested that lorazepam is not effective in treating the acute mania when compared to clonazepam.[20] Benzodiazepines should be considered primarily for desired ultra-short-term sedation of acutely agitated patients but not for augmentation of antipsychotics in the medium- and long term pharmacotherapy of schizophrenia and related disorders.[21]

Commonly used anticonvulsants drugs were sodium valproate and carbamazepine. Sodium valproate was used as off-label indications for treating mood control mania, mixed episode, for maintenance treatment of bipolar disorder and schizoaffective disorder. Sodium valproate has reported to reduce impulsive aggression in some studies.[22-24] Other psychiatric conditions such as alcohol and benzodiazepine dependence/abstinence, obesity, eating disorder has also been treated by antiepileptic drugs. Valproate replaced lithium since it shows dominance in certain bipolar patient.[25]

Clozapine, quatiapine are not mentioned in National Formulary of India (NFI)-2016 edition. However, in our study, they were used as off-label drugs. In one randomized clinical trial study, clozapine was found to be superior antipsychotic drug for the management of severely ill schizophrenic and early treatment of first episode of schizophrenic patients and who fail to respond adequately to standard drugs.[26,27]

In our study, 7% of tricyclic antidepressant (TCA) like imipramine and amitryptiline were prescribed as off-label drugs. Studies have shown that, TCA, are prescribed for pain management as an adjunct to other medications for neuropathic conditions and at lower dosages than those used for treating depression.[28] In our study, TCA were significantly prescribed for comorbities like migraine and headache.

To counteract adverse effect of psychotropic drugs, drugs like multivitamins, laxatives, GI protective agents and non steroidal anti inflammatory were prescribed whose usage was similar to the findings shown in previous studies.[12,19]

We found no significant difference between the age, gender, psychiatry disorder, comorbidities and off-label prescribing using multiple logistic regression models. Our data were different from those results found in study by Kharadi et al in India.[11]

Even though the present study was conducted with the appropriate statistical methodology, the results should be interpreted with caution considering few limitations of the study. The first limitation is that the present study was conducted only in one tertiary care hospital. Hence, it is recommended that further studies should be conducted at various clinical setups to make the result more generalized and justifiable. In the present study, we used National Formulary of India (NFI) - 2016 edition, in which drugs like clozapine and quetiapine were not included as off label drugs as compared to British National Formulary (BNF) - 2011 edition.[29] These findings suggest over estimation of prescribing such drugs as off-label. Hence, it is recommended that the revision should be made in NFI to include these drugs as off- label.

CONCLUSION

In our present study, all the drugs were prescribed by generic name which indicates rational prescription. The percentage of off-label drugs used in our study was 19.85%. The most frequently used off-label drugs was trihexiphenidyl HCL followed by clozapine, clonazepam and sodium valproate. The use of off-label drugs in psychiatric disorder has been reportedly increasing which warrant National Drug Regulatory authorities to review and revise safe administration, of such drugs.

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