



## Evaluation of off Label Drug Use in the Outpatient Department of a Psychiatry Hospital

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### ABSTRACT

Off-label practice, the use of a drug outside the Food and Drug Administration licensing terms has been widespread in the medical field, particularly in psychiatry. Off-label drug use involves prescribing medications for indications or using a dosage or dosage form, that have not been approved by Food and Drug Administration. Our objective was to evaluate the off-label drug use in the psychiatry outpatient department. A prospective randomized study was conducted in a period of 3 months. Data was collected with a well structured data collection form which includes age, gender, OP number, past medical and medication history, diagnosis and treatment full details on medications like dose, route, frequency and duration. All the prescriptions were analyzed according to Food and Drug Administration license. A total of 570 subjects were included in study with mean age 34.795 (6-90 year). Male patient were dominating as 329 in number (57.71%). The major diagnosis was schizophrenia 185 (32.45). Out of total 570 patients 183 (32.09%) received at least one off-label drug. Off-label prescribing was significantly more common in 21-40 age group, 159 (27.89%). The most commonly prescribed off-label drug was trihexyphenidyl (27.97%) The most frequently used benzodiazepine was clonazepam (17.64%) and lorazepam (16.78%). Out of total 1646 drugs, the most common off-label drug prescribing was for diagnosis BPAD, 236 (14.33). Off-label use is very common in psychiatry field. The most frequently used off-label drugs were trihexyphenidyl, benzodiazepine and valproate. Physicians should be prescribed with proper evidence.

**Keywords:** Off-label, psychiatry, licensed, psychopharmacotherapy.

### INTRODUCTION

The role of Food and Drug Administration is to approve only safe and effective medications for specific indications. The approval should be given after proper evaluation on the evidences of clinical trial, animal studies or other *in vitro* studies.<sup>1</sup> Food and Drug Administration strictly classified the various drugs into labeled and off labeled groups.

Off-label drug prescribing can be defined as the practicing of a drug outside its regulatory labeling.<sup>1,2</sup> Simply it can be explained in terms of four D's-Dose and duration of the drug and demographics (age, right drug for specific indication) of the patient. Among them, the most frequent is prescribing a drug in a manner different from that approved by Food and Drug Administration.<sup>1,2</sup> It can also be applied to use of medication outside dose range, prescribing a drug for longer duration and use of drug apart from the specified age group.<sup>3</sup>

Radley reported that at least 21 prescriptions were prescribed as off-label.<sup>4</sup> Off-label practice can be justified by various factors, primarily when the approved treatments have failed to achieve the goal. Secondly, lack of data on a drug for specific population (eg: Pediatric, geriatric or pregnant patients) and thirdly when an emergency or life healthy medical condition occurs, most available and logical treatment can be given.<sup>5</sup>

In the mean way it also have negative consequences like lack of valid information on safe and efficacy of the particular off-label drug and also sometimes use of

expensive off-label drugs may increase the health care cost.

Psycho pharmacotherapy is essential of the management of wide range of psychiatric conditions. Even though many licensed psychotropic agents are available, the patients remain in their psychotic symptoms even after continuous treatment. This paved way for the physician to prescribe unlicensed drugs. Off-label use has become common in psychiatry. Reason for off-label use are lack of clinical trials since psychiatric drugs are inherently difficult to study, also there is often similarities in the symptoms of different disease states which has lead physician to use approved drug for the unapproved indication.<sup>5</sup> 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.<sup>6</sup> Goal of our study was to determine the prevalence of the off-label drug use in outpatient department of psychiatry.

### MATERIALS AND METHODS

A prospective randomized study was conducted in psychiatric outpatient department of neuropsychiatry hospital for the period of three months from December 2015 to March 2016. Study was approved by Institutional Ethic Committee. Informed consent was obtained from the patient or patient guardian who is willing to enroll in the study.

Data collection include age, gender, OP number, past medical and medication history, diagnosis and treatment



full details on medications like dose, route, frequency and duration.

All the records were checked with Food and Drug Administration approved label. The data was entered and analyzed in MS Excel.

## RESULTS

A total of 570 subjects were included in study with mean age 34.795 (6-90 year). Male patients were dominating as

329 in number (57.71%). The major diagnosis was schizophrenia 185 (32.45%) followed by Bipolar Affective Disorder 171 (30.0%), depression 121 (21.22%), Obsessive Compulsive Disorder 37 (6.49%) and mania 19 (3%).

Other morbidities like affective disorder, dissociative disorder, psychosis, mild mental retardation, nanopsychosis and insomnia also comprises 37 in number (6.49%). The entire demographic and morbidity pattern are presented in Table 1.

**Table 1:** Demographics of Psychiatric Patients Based on Off-Label

Variables	No. of Patients	No. of Labeled Drugs	No. of Off-labeled Drugs
<b>Gender</b>			
Male	329	212	110
Female	241	168	73
<b>Age</b>			
0-20	92	53	39
21-40	326	167	159
41-60	113	57	56
61-80	28	19	9
Above 80	11	7	4
<b>Morbidities</b>			
Schizophrenia	185	103	82
Depression	121	67	54
BPAD	171	98	65
OCD	37	22	15
Mania	19	11	8
Others	37	21	16
<b>Comorbidities</b>			
DM	2	1	1
HT	2	2	0
Seizures	3	2	1
CVS disorders	4	3	1
Others	52	28	22

BPAD: Bipolar Affective Disorder, OCD: Obsessive Compulsive Disorder, DM: Diabetes Mellitus, HT: Hypertension

A total of 1646 drugs were prescribed out of which 764 were labeled antipsychotics drugs (46.41%).

The most commonly prescribed psychotropic drug was risperidone 175 (22.90%) followed by fluoxetine 129, imipramine 96 (12.56%) and haloperidol 86 (11.25%). Overall off-label prescribing was 697 (42.34 %) [Figure 1]. Out of total 570 patients 183 (32.09%) received at least one off-label drug [Figure 2].

Off-label prescribing was significantly more common in 21-40 age group, 159 (27.89%). Off-label use was more frequent in patients with schizophrenia 82 (14.38%) followed by Bipolar Affective Disorder 65 (11.40%) and depression 54 (9.47%).

The most commonly prescribed off label drug was trihexyphenidyl. As per hospital guideline, trihexyphenidyl has to be prescribed only for first 2 months of the

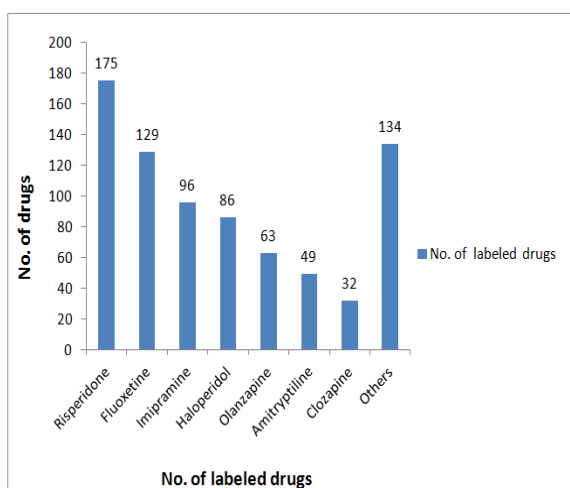
treatment. But in our study, off label prescribing was 195 (27.97%) whereas 83 (5.04%) were only prescribed accordingly.

According to Food and Drug Administration, benzodiazepine is allowed to prescribe only for initial four weeks of the psychotherapy. The most frequently used benzodiazepine was clonazepam and lorazepam.

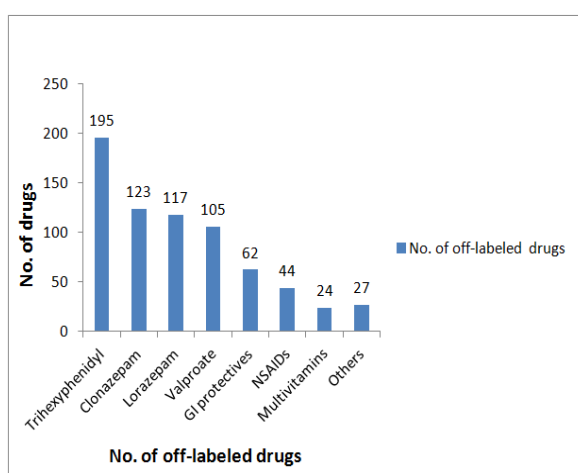
The number of off-label prescribing of clonazepam was 123 (17.64%) while only 53 (3.21 %) was prescribed as per regulation. In case of lorazepam the prevalence was 117 (16.78%) as off-label and only 49 (2.97%) was prescribed appropriately.

Out of total 1646 drugs, the most common off-label drug prescribing was for diagnosis Bipolar Affective Disorder, 236 (14.33%) followed by schizophrenia 232 (14.09 %) and depression 148 (8.99%) [Figure 3].

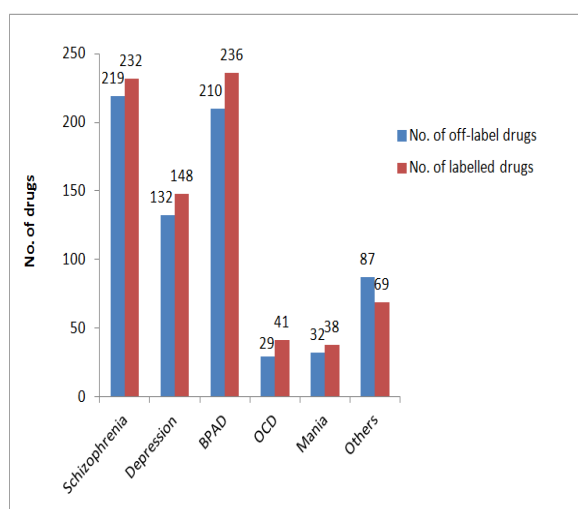




**Figure 1:** Distribution of Labeled Drugs in Psychiatry (n=764)



**Figure 2:** Distribution of Off-labeled Drugs in Psychiatry (n=697)



**Figure 3:** Comparison of Off-labeled and Labeled Drugs

## DISCUSSION

Our study analyzed the use of off-label drugs in the outpatient department of neuropsychiatry hospital. The mean age group (34.597) was similar to the other Indian outpatient study, which was 33.9 years.<sup>7</sup> Various studies

reported that off-label antipsychotic use has been increasing in all age groups. Male subjects were slightly dominating with a proportion of 1:2:1 similar to the previous studies.<sup>8,9</sup>

Most frequent diagnosis was schizophrenia and bipolar disorder. Other authors also have reported major depressive illness and bipolar disorders as the common outpatient visits of psychiatric disorders. In our study, the mean number of drugs prescribed per patient was 2.88 which were similar to the earlier studies which reported as 2.01.<sup>8</sup>

Both off-label as well as labeled prescribing was equally practicing in our hospital, 42.34% and 46.41% respectively. The major off-label drug was trihexyphenidyl, an anticholinergic drug (27.97%). Extrapyramidal symptoms are the serious side effects caused by many antipsychotics resulting in painful and devastating state.<sup>10</sup> Anticholinergics are considered to be the primary treatment for extrapyramidal symptoms which includes trihexyphenidyl. The symptoms vary from minimum discomfort to permanent involuntary muscular movement, which occurs after the first dose and later progress as treatment proceeds.<sup>11</sup> Along with anticholinergics, benzodiazepines and antiparkinsonism agents also have been used as the prophylactic and the first line regimen for many extrapyramidal symptoms.<sup>12-14</sup> But the anticholinergics can produce risks such as dry mouth, blurred vision, constipation, tachycardia, dizziness, confusion, dependence and psychosis. Sometimes the drug itself can provoke tardive dyskinesia.<sup>12,13,15</sup>

Benzodiazepines mainly clonazepam and lorazepam comprises a bigger portion of off labeling (35.29%). Individually clonazepam contributes 17.64% were as lorazepam 16.78%. Haw showed that over 90% of the benzodiazepines prescribing was off-label.<sup>16</sup> Benzodiazepines have been considered as the treatment choice for catatonia since it is very effective and safe.<sup>17</sup> It also has been used for reducing the neuroleptic induced side effects such as akathisia or tardive dyskinesia. Nowadays, benzodiazepines have been used apart from the approved indication such as depression.<sup>18</sup> Even though benzodiazepines are very effective in treating various psychiatric conditions like insomnia, anxiety, panic disorder and alcohol withdrawal syndrome; they are prone to produce adverse effects.<sup>19</sup> Long term benzodiazepines use may cause loss of effectiveness, produce tolerance, dependence as well as withdrawal symptoms. Action of clonazepam includes its serotonin agonistic activity (which benefits in treatment of mania); anti convulsive effects in subclinical epilepsy and anti anxiety effects.<sup>20,21</sup> Curtin suggested that lorazepam is not effective in treating the acute mania when compared to clonazepam.<sup>22</sup>

Anticonvulsants have been widely used by the psychiatrists as off-label drug. Carbamazepine and valproate are Food and Drug Administration approved for

the treating acute manic or mixed episode and maintenance treatment of bipolar I disorder in adults. Many psychiatrists are prescribing these drugs for the indications – mania and schizoaffective disorders. Various studies demonstrate that they produce significant reduction in manic symptoms after 3 weeks of treatment. They are also added to potentiate clozapine for the treatment resistant schizophrenia.<sup>23</sup> Other psychiatric conditions such as alcohol and benzodiazepine dependence/abstinence, obesity, eating disorder has also treated by antiepileptic drugs.<sup>24-26</sup> Antiepileptic drugs potentiate the action of antidepressants in patients with who partially responds to agitation or irritability.<sup>27</sup> Now, antiepileptic are used extensively as adjuvant with antipsychotics in the treatment of schizophrenia.<sup>24,28</sup> Divalproex is approved for acute mania whereas its extended release is indicated for both mania and mixed episodes.<sup>29</sup> Valproate replaced lithium since it shows dominance in certain bipolar patients.<sup>30-32</sup> Various studies suggest that valproic acid have been useful when mixed episode and co morbid substance abuse was there.<sup>30-34</sup> Valproic acid showed longer duration as prophylactic therapy. Negative results were also showed for the use of valproate in decreasing impulsive aggression.<sup>35</sup> Although valproate is not approved for depression, it showed effective in certain patients.<sup>36</sup> Even though antiepileptic drugs have been used as substitute for selective serotonin reuptake inhibitors and benzodiazepines for anxiety disorder, the evidence showed that they are not efficacious.<sup>37</sup>

To withstand the Adverse Drug Reactions caused by psychotropic drugs, certain groups of drugs like gastrointestinal protective, Non Steroidal Anti Inflammatory drugs, multivitamins were also given to the patients. Evidences are there supporting the usage of these drugs in the earlier studies.<sup>8</sup>

Limitation of our study includes small duration and shortage of similar Indian studies, so that the results of our study were not comparable with Indian set-up. Physician should practice medications only with support of proper evidence. Psychiatrists should educate themselves about the off-label practice and prescribing has to be done after analyzing the benefit and risk ratio of each drug.

## CONCLUSION

Off-label use is extensive in the present scenario especially in the psychiatric field. The most commonly used off-label drugs were trihexyphenidyl, benzodiazepine and valproate. Physicians should be updated on the new trends in psychiatry.

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