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RESEARCH ARTICLE

Evaluation of patterns and predictors of off-label prescribing of antidepressants in psychiatry at a tertiary care hospital - An analytical cross-sectional study

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ABSTRACT

Background: Off-label drug prescribing is commonly seen all medical fields including psychiatry. A regular auditing and publishing of off-label drug prescribing is important as it provides strong scientific evidence for the clinicians on the effectiveness and acceptability of these proposed treatments. **Aims and Objective**: To evaluate the pattern and predictors of off-label prescribing of antidepressants in psychiatry was taken up. **Materials and Methods:** After obtaining the permission from Institutional Ethics Committee, an analytical cross-sectional study was conducted among patients attending psychiatry outpatient department for 6 months. Demographic and drug data were noted and analyzed for off-label drug use as per Food Drug Administration approved indication. Chi-square test and Student's *t*-test were used to compare the off-label and approved indication groups. Multivariate binary logistic regression model was used to determine the predictors of off-label prescribing. **Results:** A total of 238 antidepressants were prescribed for 200 patients, of which 42.8% were used for off-label indication. Fluoxetine 44.1% and escitalopram 42.1% were the most frequently prescribed antidepressants in off-label manner. The off label indications noted was somatoform disorder (12.5%), followed by generalized anxiety disorder (8.5%). There was significant causal association between off-label prescribing and number of antidepressant (odds ratio [OR] - 15.43, 95% confidence interval [CI] - 3.49-89.02, $P < 0.05$) and non-depressant use (OR - 74.37, 95% CI - 25.4-293.71, $P \leq 0.05$). **Conclusion:** Off-label use of antidepressants was 42.8% in this study. A number of antidepressants and non-depressant uses were the significant predictors of off-label prescribing in our hospital.

KEY WORDS: Antidepressant; Off-label Use; Non-depression Use; Psychiatry

INTRODUCTION

Drugs have to undergo rigorous scrutiny before marketing approval in the form of *in vitro* studies, animal studies, and clinical trials. Trial data provide specific information on approved indications, appropriate dosing and the specific populations for its use.[1] The prescribing of drugs for non-Food Drug Administration (FDA) approved uses is called as "off-label prescribing."[2] Off-label use also includes the use of pharmaceutical drugs in unapproved age group, dosage, or form of administration.[3]

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Off-label prescribing has gained popularity as the process of obtaining modifications to a product license of an existing drug is lengthy and costly. The other factors motivating off-label drug use could be that a particular drug has not been studied in a specific population (e.g. pediatrics and geriatrics). In terminally ill patients, clinicians may use any

available and logical treatment, whether approved or not. If any two conditions have similar pathologic features, then drug approved in one condition could be used in another condition without specific approval. Approval of a new use for an old drug often results in high cost–benefit ratio for FDA.[2] Off-label prescribing is a common in every field of medicine. It is most commonly seen in pediatric population (80-90%), followed by drug use in cancer (56%) and AIDS (40%).[2]

Last decade has seen increased prescribing of psychotropic drugs.[4,5] Off-label use of drugs in psychiatry setting is a very common feature.[6-8] Patients with psychiatric disorders are often excluded from clinical trials, and the crossover in symptoms from disease state to disease state leading to use of medications for additional unapproved indications. It has been reported that 90% of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) do not have FDA approved medications. The most common mode of off-label prescribing in psychiatry department is for unapproved indication, dose, and altered population.[9,10] The most common psychiatric indications for off-label prescribing are depression, obsessive compulsive disorder (OCD), post-traumatic disorder, and personality traits.[11] A survey of more than 1000 patients receiving antidepressant drugs in Canada found that a majority of drug use (56%) was off-label.[12] Hanlon et al. have recently observed that antidepressants were prescribed in 42% of elderly patients without a clear history of depression.[13]

Hence, a regular audit on off-label use of drugs should be encouraged, as the data provide scientific evidence on the efficacy and safety of these drugs for off-label prescriptions. Literature survey revealed only one study from Gujarat, India, by Kharadi et al. on off-label use of psychotropic medications.[14] Hence, this study was taken with a hypothesis that off-label prescribing was common in the department of psychiatry of our hospital.

MATERIALS AND METHODS

This was an analytical cross-sectional study conducted in the psychiatry outpatient department for 6 months from January 21 to June 24, 2015 of Bangalore Medical College and Research Institute Hospital, Bengaluru, India, a tertiary care teaching hospital. After obtaining informed consent from the participants aged >18 years, prescription of 200 consecutive patients who were prescribed with antidepressant drugs was independently reviewed for relevant data by two investigators. All relevant data on demographics (age, gender, and religion), clinical characteristics (complete diagnosis and comorbid conditions), and treatment (drugs prescribed) were collected in a specially designed case record form.

The study was conducted after obtaining approval from the Institutional Ethics Committee of Bangalore Medical College and Research Institute and done in compliance with the Declaration of Helsinki and Indian Good Clinical Practice guideline.

Definitions

Based on definitions used in the literature, we a priori defined an off-label use as "Use of drugs for indication, dose, dosage form, duration of therapy, and patients not mentioned in the approved labeling" as per FDA.

Off-label Prescribing Assessment and Analysis

Off-label prescribing was assessed for indication, dose, duration and dosage form as per FDA approved indications.[15] Each off-label prescribing was assessed for indication, dose, duration, and dosage form independently by two investigators and the level of agreement determined. Disagreement among the two reviewers used to be resolved after discussion with a review panel. The review panel consisted of a psychiatrist and a research officer. Disagreements were resolved and included in the final analysis. The total number of drugs prescribed for each patient was considered in the calculation of the total number of drugs prescribed in the outpatient department. Each drug was considered only once for the same patient for the analysis. The data of patients were further subdivided into two groups based on the off-label prescribing: Those patients who were prescribed with an antidepressant in off-label manner during the study period and those who were prescribed with antidepressant according to FDA approved indication. These two groups of patients were compared for various characteristics.

Predictors of Off-label Prescribing

Data on demographics (age, gender), psychiatric co-morbid illness (schizophrenia, alcohol dependence syndrome, dysthymia, dissociation disorder and psychosis), number of antidepressants prescribed, and non-depressant uses of antidepressant were analyzed to identify the potential predictors of off-label prescribing.

Statistical Analysis

The data collected were analyzed using descriptive statistics to study the characteristics of the off-label prescribing. Results were presented as percentages, as mean±standard deviation for continuous parametric variables and as the median and inter quartile range for continuous nonparametric variables. Comparisons between the off-label prescribing group and the approved prescribing groups were performed using the *t*-test and chi-square test as appropriate. $P < 0.05$ was considered as statistically significant. Multivariate binary logistic regression model was used to control the multiple predictors for off-label prescribing using forward stepwise approach. The explanatory variables considered for the first step of

the logistic regression analysis included attributes such as data on demographics (age, gender), psychiatric co-morbid illness (schizophrenia, alcohol dependence syndrome, dysthymia, dissociation disorder and psychosis), number of antidepressants prescribed, and non-depressant use of antidepressant. Variables that were significant in the first step of analysis were subjected to multivariate logistic regression analysis. Odds ratio (OR) and 95% confidence interval (CI) were calculated for each predictor. R software version 3.2.0 was used for statistical analysis.

RESULTS

Demographic Characteristics

A total of 200 consecutive patients attended the psychiatry outpatient department were enrolled. Among these 96 (48%) patients were noted have off-label use of one antidepressant and 6 (3%) patients received two antidepressants for off label use. Among these 200 patients, 112 (59.09%) were males. Approximately, 58 (52.7%) patients belonged to Hindu community, 35 (31.82%) to Muslim community, and 17 (15.45%) patients were Christian. The mean age of the patients in the off-label and approved indication groups was (35.45 ± 7.49 vs. 35.31 ± 8.14 years, $P = 0.37$), respectively. The patients in the off-label group had received a significantly more medications (1.91 ± 0.31 vs. 1.88 ± 0.9, $P < 0.05$) than patients in the approved indication group (Table 1).

Among 200 patients, the most common comorbid conditions were schizophrenia (17 patients, 8.5%), psychosis (26 patients, 13%), alcohol dependence syndrome (15 patients, 7.5%), dysthymia (7 patients, 3.5%), and dissociation disorder (6 patients, 3%). Comparison of the comorbidities between patients with off-label group and those prescribed according to approved labeling (label group) are presented in Table 2. The most common indication for antidepressant prescriptions was moderate depressive disorder 44 (22%) followed by severe depression 27 (26.8%), generalized anxiety disorder (GAD) 19 (12%), social anxiety disorder 18 (9%), and somatoform disorder 25 (14%).

Inter-reviewer Agreement

Two reviewers independently assessed the off-label prescribing according to the FDA approved indication chart. The Cohen's weighted kappa score for inter reviewer agreement was 0.525 for off-label prescribing. Thus, there was a moderate level of agreement between the reviewers for all parameters assessed.

Drug Data Analysis

Selective serotonin reuptake inhibitors (SSRIs) were the frequently prescribed psychotropic drugs. Fluoxetine (45%) was the most frequently prescribed SSRI, followed by escitalopram (29%). Amitriptyline (18%) was the most commonly prescribed tricyclic antidepressant. Mirtazapine (3%) was the most commonly prescribed atypical antidepressant. Venlafaxine (2%) was the most commonly prescribed serotonin-noradrenaline reuptake inhibitor. Commonly prescribed comedications were antipsychotics (7.83%), benzodiazepine (19.84%), and central anticholinergics (6.53%) (Figure 1).

Table 1: Comparison of characteristics between the off-label and labelled indication groups of patients in the psychiatry outpatient department

Characteristics	Off-label group (*n*=96)	Label group (*n*=104)	*P* value
Age, mean±SD	35.45±7.49	35.31±8.14	0.37≠
Gender			
Male (%)	53 (26.5)	59 (29.5)	0.94*
Female (%)	43 (21.5)	45 (22.5)	
Number of psychiatric co-morbid illness, mean±SD	1.08±0.89	1.05±1.08	0.19≠
Number of medications, mean±SD	1.91±0.31	1.88±0.95	0.01≠

Data are given as the number (n) of patients with the percentage in parentheses, or as the mean±SD, *Chi-square test for significance, ≠*t*-test for significance, $P<0.05$ considered as significant.
SD: Standard deviation

Table 2: Comparison of comorbidities between the off-label and labelled indication groups of patients in the psychiatry outpatient department

Psychiatric comorbid illness	Off-label group (*n*=96)	Label-group (*n*=104)	*P* value*
Schizophrenia (%)	8 (4)	9 (4.5)	0.29
Psychosis (%)	10 (5)	16 (8)	0.40
Dysthymia (%)	3 (1.5)	4 (2)	0.41
Alcohol dependence syndrome (%)	6 (3)	9 (4.5)	0.70
Dissociation disorder (%)	3 (1.5)	3 (1.5)	0.92

Data are given as the number (n) of patients with the percentage in parentheses, *Chi-square test for significance, $P<0.05$ considered as significant

Characteristics of Off-label Prescribing

Out of 238 antidepressant prescriptions, 102 (42.8%) drugs were prescribed in off-label manner. Of 200 patients, 90 (45%) patients received one off-label drug as per FDA approved indications. The antidepressant most frequently prescribed in off-label manner was fluoxetine (44.1%), escitalopram (42.1%), and amitriptyline (13.72%) as shown in Table 3. Off label indications for antidepressants included, GAD, social anxiety disorder and panic disorder (Table 3).

Characteristics of Prescribing for Non-depressant Indications

Among the 238 antidepressant drugs, 111 (46.6%) were used for indications other than depression (non-depressant use). Fluoxetine (43.24%) was used mostly for non-depressant indications, followed by escitalopram (40.54%). GAD (17.11%), social anxiety disorder (16.21%), and somatoform disorder (22.52%) were the most commonly cited indication other than depression (Table 4).

Drug Utilization Comparison

Non-depressant uses were significantly higher with escitalopram (44%, $P < 0.05$). Amitriptyline was significantly associated with polytherapy of antidepressants (23%, $P < 0.05$). Off-label uses were significantly noted with escitalopram (62%, $P < 0.05$). Characteristics of the antidepressants prescribed frequently in off-label manner were compared in Table 5.

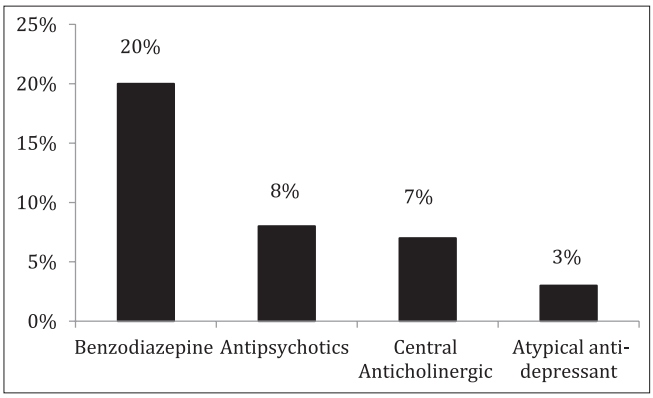

Figure 1: Commonly prescribed psychotropic comedications

Predictors for Off-label Prescribing in Psychiatry Out-patient Department

The multivariate logistic regression analysis showed that, increase in the number of antidepressants, increased the off label use (OR - 15.43, 95% CI - 3.49-89.02, $P < 0.05$) of antidepressants. Increase in the non-depressant use of antidepressants also increased the off-label use (OR - 74.37, 95% CI - 25.4-293.71, $P \leq 0.05$) (Table 6).

DISCUSSION

The off-label prescribing of antidepressants was noted to be 42.8% in this study. Fluoxetine, followed by escitalopram were most commonly prescribed in off label manner. A number of antidepressants and non-depressant use were significantly associated with off-label prescribing of antidepressants.

In this study, a mean age of the patients was noted to be 35, and the male:female ratio was 1.6:1, which is comparable to other Indian studies.[16,17] Mean number of psychotropic drugs prescribed per patient was 1.91±0.901 which was

Table 3: Off-label uses of antidepressants (*n*=102)

Drug name (total)	Off label indication								
	Adjustment disorder	GAD	Panic attack	PTSD	Social anxiety disorder	Somatoform disorder	Acute stress reaction	Phobic disorder	OCD
Fluoxetine (*n*=45)	7	17		5	7	8	-	1	-
Escitalopram (*n*=43)	4	-	6	5	9	3	4	3	9
Amitriptyline (*n*=14)	-	-	-	-	-	14	-		-

GAD: Generalized anxiety disorder, PTSD: Posttraumatic stress disorder, OCD: Obsessive compulsive disorder

Table 4: Indications of non-depressant uses of antidepressants (*n*=111)

Name of the drug	GAD	Social anxiety disorder	Panic disorder	Somatoform disorder	Adjustment disorder	PTSD	OCD	Acute stress reaction	Phobic disorder
Fluoxetine (*n*=48)	17	7	2	8	7	5	1	-	1
Escitalopram (*n*=45)	2	9	6	3	4	5	9	4	3
Amitriptyline (*n*=14)	-	-	-	14	-	-	-	-	-
Paroxetine (*n*=4)	-	2	2	-	-	-	-	-	-

GAD: Generalized anxiety disorder, PTSD: Posttraumatic stress disorder, OCD: Obsessive compulsive disorder

Table 5: Comparison of characteristics of antidepressants frequently prescribed in off-label manner

Variables	Fluoxetine (*n*=108)	Escitalopram (*n*=70)	Amitriptyline (*n*=42)	*P* value*
Non-depression use (%)	48 (44)	45 (64.28)	14 (34)	<0.05
Off-label use (%)	45 (42)	43 (61.5)	14 (34)	<0.05
Polytherapy (%)	24 (23)	18 (26)	22 (64)	<0.05

Data are given as the number (n) of patients with the percentage in parentheses. *Chi-square test for significance, $P<0.05$ considered as significant

Table 6: Predictors for off-label prescribing in the psychiatry outpatient department

Variables	β coefficients	*P* value	OR	95% CI
Age	0.208	0.39	1.02	0.97-1.07
Gender (male)	−0.623	0.17	0.54	0.21-1.30
Number of antidepressant	2.73	<0.05	15.33	3.49-89.02
Psychiatric comorbid illness	0.308	0.24	1.36	0.82-2.35
Non-depressant use	4.30	<0.05	74.37	25.4-293.71

OR: Odds ratio, CI: Confidence interval

slightly more as compared to the study conducted by Thakkar et al. in Mumbai, India that reported 1.79 ± 1.02.[18] The slight difference could be attributed to difference in prescribing practices and associated co-morbid conditions. A multi-centric study conducted across 16 centers in India to evaluate the prescribing pattern of antidepressants, reported that SSRIs was the most commonly preferred antidepressant across India. The result is comparable to our study, but the most commonly prescribed SSRI was escitalopram (40%) in our study as against fluoxetine (55%) in the multi-centric study.[16] Grover et al. also showed that Mirtazapine was the commonly prescribed atypical antidepressant across India, which matches with our study.[16] 42.8% of the antidepressants were noted to be prescribed in off-label manner. Kharadi et al. evaluated the off label use of psychotropic medication in a tertiary care center at Gujarat, reported 39.5% drugs were prescribed in off-label manner.[14] The off label prescribing of SSRI was 39.1%, which is slightly higher compared to 34.4% reported by Volkers et al. in Dutch General Practice.[19] This could be influenced by differences in the study population, prescribing practices, and availability of psychotropic drugs in the hospital. The availability of more number of antidepressants in the recent years could also be one of the factors responsible for off label prescribing. Fluoxetine was mainly prescribed in off-label manner for GAD, somatoform disorder, followed by Social anxiety disorder. Zou et al. analyzed fifteen open-label, non-placebo trials to evaluate the efficacy and safety of fluoxetine in GAD in Chinese patients and reported that fluoxetine had rapid onset of action (approximately 1-2 weeks), well tolerated, effective for maintenance therapy, and its efficacy was comparable to other anxiolytic agents such as diazepam, doxepin, and amitriptyline.[20] Escitalopram was noted to be prescribed frequently for off – label indications, mainly OCD, Social anxiety disorder and Panic disorder. Although SSRIs are indicated in OCD, escitalopram has not been approved by FDA. A case study by Kirkcaldy et al. reported a favorable outcome for Escitalopram in OCD. Escitalopram has many advantages over other SSRIs that favor its use in off-label indications.[21] It consists of only the S isomer and hence targets the organization of the nervous system more specifically than a racemic mixture. It is the most selective of the SSRIs and has shown efficacy in other anxiety disorders including GAD, social anxiety disorder and Panic disorder.[22]

We found significant association between the number of antidepressants and off-label prescribing (OR - 15.33, CI - 3.42-89, $P < 0.05$), using multiple logistic regression model which matches with the results of the study conducted by Kharadi et al. in Gujarat.[14] Non-depressant use was also a significant determinant of off-label prescribing (OR - 74, 95% CI - 95-274, p<0.05). A lack of availability of approved drugs for 90% of the DSM-IV diagnosed condition and cross-over of symptoms in disease states in psychiatry could be responsible for the same.[9,10]

In India, we identified only one study from Gujarat that aimed at identifying the pattern of off label prescribing in psychiatry.[14] Hence, this study adds to the evidence of off-label prescribing from India which is limited at present. We also evaluated the predictors of off label prescribing that may further rationalize off-label prescribing. The limitations of our study include smaller sample size, short study period and lack of follow-up details of the patients. Larger sample size would have helped us to generalize our study results. Follow-up of these patients would have provided more information about the safety and efficacy of the antidepressants prescribed in off-label manner. FDA states that clinicians can prescribe off-label drugs provided they are aware of the benefits of such prescribing practices. The Royal College of Psychiatrists have provided a set of recommendations that can be followed to ensure appropriateness of off-label prescribing.[5]

CONCLUSION

Off-label drug prescribing is prevalent in psychiatric outpatient department. Fluoxetine and escitalopram were found to be the most frequently used drugs in off-label manner. A number of antidepressants and non-depressant uses were the significant predictors of off-label prescribing. There is a need to raise awareness among psychiatrists and to encourage evidence-based off-label drug use.

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