

Off-label drugs use in neurology outpatient department: A prospective study at a tertiary care teaching hospital

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Abstract

Background: Off-label drug use refers to any use of an approved or cleared drug that is not included in that product's approved labeling or cleared indications for use. It may be in terms of indication, age group, dosage, or route of administration. Off-label drug prescriptions are common neurology practice.

Aim: The aim of the study is to evaluate the prevalence pattern of off-label drug use in neurology.

Subjects and Methods: A prospective, observational, cross-sectional study was carried out in the neurology outpatient department of tertiary care teaching hospital. Data of patients above 18 years were recorded after obtaining their informed consent. The National Formulary of India (NFI) and British National Formulary (BNF) guidelines were used as tools for evaluation of the prevalence of off-label drug use.

Results: A total of 709 drugs were recorded from the prescription data of 205 patients collected in the duration of 2 months. The results reported 145 (20.45%) and 317 (44.71%) drugs as off-label as per the NFI and BNF, respectively. Prescriptions with minimum 1 off-label drug use were 78.05% – BNF and 46.83% – NFI. The indication was one of the most common causes of drugs being off-label. Out of the total 317 off-label drug uses reported, 84 were unlicensed drug use as per the BNF. There is strong and positive correlation established between the age of the patients, number of drugs prescribed, and total off-label drugs prescribed per patient in the given study. The most common off-label drug use noted was with clonazepam and amitriptyline.

Conclusion: Off-label prescriptions practice is common in the field of neurology.

Keywords: Amitriptyline, clonazepam, neurology, off-label

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INTRODUCTION

According to the US Food and Drug Administration (FDA), the terms “unapproved new use” and “off-label use” interchangeably refer to any use of an approved or cleared drug that is not included in that product's approved labeling or cleared indications for use.^[1] Off-label use is the use of pharmaceutical drugs for an indication, age group, dosage,

or route of administration that is not approved by the regulatory agencies and is not mentioned in the prescribing information for the drug.

Off-label use is not illegal unless it violates safety regulation and ethical guidelines. A clinician's prescription may vary

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from the guidelines by regulatory authorities based on his clinical experience and data backed by strong medical rationale and scientific evidence from various sources.

Off-label prescriptions are observed in cases where standard therapy fails or where limited therapeutic options available for the conditions.^[2]

If frequent use of specific off-label drug is reported in scientific papers, clinical trials are conducted by pharmaceuticals, and it is possible for off-label uses to eventually get approved by the regulatory authorities. This provides a better reliability in utilizing medicines with assured safety and efficacy.

Frequent off-label drug uses have been reported for antipsychotics, antiepileptics, and in several studies of pediatric age group.^[3-5] A recent survey conducted in Spain on off-label use of drugs provided data of maximum use of off-label drugs in the fields of oncology, neurology, rheumatology, nephrology, and hematology.^[6] Off-label use of drugs is not something new in Neurology. A study conducted in the year of 2001 revealed that more than 50% of all prescriptions for anticonvulsants issued by office-based physicians were off-label drugs. A similar study conducted in 2004 depicted that an estimated 47% of prescriptions issued over 30 days from a US tertiary headache unit were for off-label indications.^[7]

Major issues associated with off-label use includes some popular drug lawsuits like “the Gabapentin issue” where Warner–Lambert pharmaceutical company was legally restricted from marketing and for promoting the drug gabapentin (neurontin) for variety of off-label indications.^[8]

This study related to off-label drug use in neurology was conducted because neurological disorders contribute to significant cause of morbidity and mortality, and lots of research works are carried out for exploring new drugs for better therapy options every year. Off-label drug use, therefore, is an established, integral, and standard part of neurological practice.^[9] Off-label monitoring and drug pattern studies in neurology could highlight such drug uses and serves as an add-on to postsale surveillance of the drugs helping the regulatory authorities to control sale of drugs preventing exploitation and associated future tragedies. With rising number of drug pattern evaluation studies and off-label drug studies which are being carried out in different aspects of clinical sciences both in abroad as well as in India, surprisingly presents a distinct lack of research on off-label use of drugs with only a few articles in India till the date.^[9-11]

Aims and objectives

The aims and objectives of this study are as follows:

- To assess the prevalence and pattern of off-label use of drugs in neurology outpatient department (OPD) of a tertiary care teaching hospital
- To evaluate off-label drug use based on various parameters such as age group of patients, frequency of prescriptions, cost-effectiveness, and indications for which it is used and to assess the parameters involved with off-label use of drugs in neurology.

SUBJECTS AND METHODS

A prospective, observational, cross-sectional study was carried out in neurology OPD of tertiary care teaching hospital over the duration of 2 months – June 2017 and August 2017. Institutional Ethics Committee approval along with permission from Hospital Superintendent and Head of Neurology Department was obtained before the commencement. All the patients above 18 years of age who attended the neurology OPD during the given time period of study were enrolled in the study after obtaining their informed consent. Complete clinical history along with demographic data and complete prescription details of recruited participants were obtained from OPD casebook and were recorded in case record form. Obtained data were entered in the master chart. Nonproprietary names for prescribed drugs under brand names were obtained using CIMS online and online drug stores such as 1 mg and Medindia. Drug details in prescriptions were compared with standard guidelines from the National Formulary of India (NFI)-2016 (New Delhi Indian Pharmacopoeia) and British National Formulary (BNF)-73rd Edition March–September 2017 (London BMJ and Pharmaceutical Press) for indication, frequency, dosage, and formulation. Off-label drug prescriptions were noted and evaluated separately under individual guidelines of BNF and NFI. Reason for off-label was noted along with remarks. Unlicensed drug uses found during the study using BNF criteria were also noted. Drug cost of the prescribed drug was calculated from online stores and CIMS online.

Data recorded in spreadsheet were analyzed using statistical tools for further comparison and analysis was carried out along with establishment of significance of correlation based on Pearson’s regression formula.

RESULTS

Of the total 205 case record data collected from the neurology OPD, male: female patient ratio was found to be 1.23 among cases with average age of 45.45 ± 16.756 years.

Out of 205 cases, follow-up cases were 143 cases (69.76%). Cases of headache (32.68%) and epilepsy prophylaxis (24.39%) contributed to majority of patients in the study.

A total of 709 drugs were evaluated with average drugs prescribed per patient being 3.05 ± 1.802 . Propranolol (37) was the most frequently prescribed drug followed by aspirin (36) and amitriptyline (36) [Table 1]. Of the 709 total drugs, 145 drugs were considered off-label as per the NFI guidelines which contribute to 20.45%, whereas 317 drugs were considered off-label as per the BNF guidelines which contribute to 44.71%. The most common cause for drugs being off-label in both NFI and BNF guidelines was “Indication” for comparison followed by “Dose” in BNF and “Frequency” in NFI [Figure 1]. Clonazepam was the most common off-label prescribed drug reported as per the NFI guidelines, other drugs reported were propranolol, amlodipine, etc., Amitriptyline was the most common off-label prescribed drug reported as per BNF guidelines for its indication followed by naproxen and aspirin, atorvastatin, etc., Among the most commonly prescribed drugs, propranolol was found to be off-label in 35.14% (13) and 32.13% (12) cases with respect to NFI and BNF guidelines, respectively [Table 1]. Out of 317 drugs reported as off-label with BNF guidelines for comparison, 84 drugs prescribed were reported unlicensed for their use. A higher number of off-label drug use was reported in prescriptions with more number of drugs [Figure 2]. A strong correlation was established between identification of off-label drugs using BNF and NFI [Figure 3].

There was strong and positive correlation established between age of patient and total off-label drugs prescribed per patient, which is highly statistically significant (Pearson correlation coefficient $r = 0.194$ and $P < 0.05$). A strong correlation between number of drugs prescribed and total off-label drugs per prescription was noted, which is also highly significant (Pearson correlation coefficient $r = 0.406$ and $r = 0.568$ and $P < 0.001$) [Table 2]. There

was no significant difference between cost of off-label and on-label drugs with difference of only 0.28% in average cost of the two groups noted in the study.

DISCUSSION

The study analyzed prescriptions of 205 cases including only OPD cases unlike a similar study in China which included both outpatient and indoor cases in neurology.^[4] The most common diagnosis in the study was epilepsy (22%) followed by migraine (13%) and tension-type headache (13%). Epilepsy was also reported

Table 1: Off-label use reported in 10 most frequently prescribed drugs

Drugs	Off-label		Total times prescribed
	NFI	BNF	
Propranolol	13	12	37
Amitriptyline	4	35	36
Aspirin	0	23	36
Naproxen	NA	35	35
Atorvastatin	NA	29	30
Pantoprazole	0	1	26
Levetiracetam	NA	1	24
Clonazepam	20	19	23
Escitalopram	7	8	21
Amlodipine	11	11	19

NA=Data not available, NFI=National Formulary of India, BNF=British National Formulary

Table 2: Statistical correlations

	Age (years)	Number of drugs	Total off-label	
			NFI	BNF
Age (years)				
Pearson correlation	1	0.219**	0.032	0.194**
Significant (two-tailed)		0.002	0.648	0.006
Number of drugs				
Pearson correlation	0.219**	1	0.406**	0.588**
Significant (two-tailed)	0.002		0.000	0.000
Total off-label NFI				
Pearson correlation	0.032	0.406**	1	0.627**
Significant (two-tailed)	0.648	0.000		0.000
Total off-label BNF				
Pearson correlation	0.194**	0.588**	0.627**	1
Significant (two-tailed)	0.006	0.000	0.000	

**Correlation is significant at the 0.01 level (two-tailed). NFI=National Formulary of India, BNF=British National Formulary

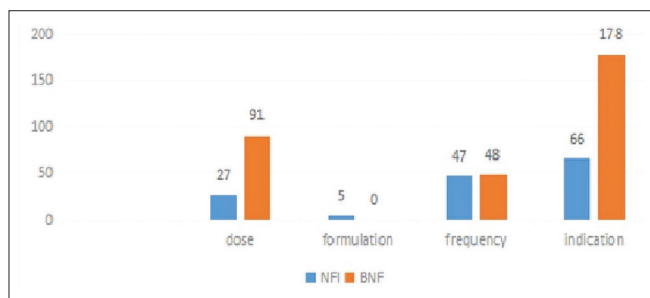


Figure 1: Criteria for drug to qualify as off-label according to the British National Formulary and National Formulary of India

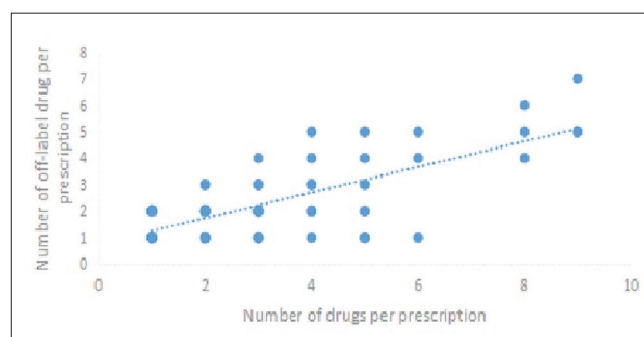


Figure 2: Off-label drug use reported out of total drugs per prescription

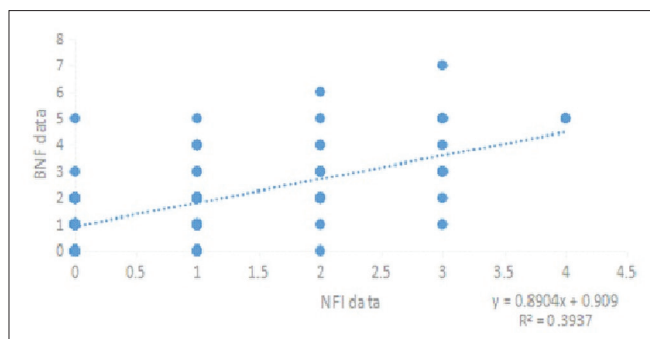


Figure 3: Comparison of off-label drugs reported as per the British National Formulary and National Formulary of India criteria

in majority of cases in a similar study conducted in pediatric neurology in India.^[11] Hypertension and diabetes served as most common comorbidities in participants included in the study which might be contributing factors for multidrug therapy and associated modifications.

Among the most commonly prescribed drugs, majority of drug prescriptions included oral formulations and drugs prescribed for 1–2 months' duration providing compliance to patient for follow-ups and prescription refills. Follow-ups were scheduled monthly or bimonthly in most of the cases. A higher number of drugs were reported off-label under the BNF guidelines (44%) as compared to NFI guidelines (20%). The percentage of off-label drug reporting is comparable to a similar study in China reporting 34.7% off-label drug use.^[2] Number of prescriptions with minimum 1 off-label drug prescribed were 32% and 30%, respectively, as per the BNF and NFI. The drug most frequently prescribed as off-label is amitriptyline as per the BNF and clonazepam as per the NFI. Mecobalamin had the highest frequency of off-label use in a study conducted in China.^[2] We have excluded multivitamins from prescription and considered them as food supplements.

According to the NFI, maximum off-label was reported in terms of “Indication” (32%) followed by “Frequency” (32%) and “Dose” (19%) which can be explained by the fact that in neurology, new use of drugs are being constantly explored so as to utilize them for newer therapy options. According to the BNF, the most common reason being “Indication” (56%) followed by “Dose” (29%) and “Frequency” (15%). “Indication” and “Frequency” are most commonly reported for off-label use in previous studies.^[2,12] The difference between average cost of the two groups was only 0.5 rupee. In our study, there was no significant correlation between cost and off-label drug prescriptions was noted.

In our study, according to the NFI guidelines, clonazepam is recorded off-label maximum times where it has been used as off-label 20 times out of 23 times prescribed. Clonazepam use as fixed-dose combination with antidepressant escitalopram was reported as off-label for its indication for its use in tension-type headache. Antianxiety effect of clonazepam may benefit the patients of tension-type headache. Clonazepam is also reported off-label for its use as add-on therapy in many cases for frequency which should be three times a day ideally.

Chlordiazepoxide is found to be extensively used along with amitriptyline as a fixed-dose combination for different types of headache where it is found to be off-label for this indication. The antianxiety effect may explain benefits of use of this drug in headache types as most of the time features of depression and anxiety are found to be associated with headache. Phenytoin was reported off-label with subtherapeutic doses in prescriptions for epilepsy prophylaxis. Other popular off-label drugs include drugs for neuropathy such as gabapentin and amitriptyline. Among top 10 most common off-label drug use noted as per the NFI, frequency (45%) and indication (40%) form the most common cause for drug being off-label.

Among drugs, only two drugs with formulation error were noted including zonisamide and tramadol. There was formulation error noted in a very popular fixed-dose combination of paracetamol and tramadol which is quite popular in chronic pain management, especially in orthopedics and neurology, despite of its use only approved for 5 days therapy only as per data referred from the FDA guidelines. Dose of paracetamol being 162.5 mg and tramadol being 75 mg are both notably subtherapeutic. This may raise a question on efficacy of drug and whether it is rational to use in management of pain or not despite of its popularity. This might result in therapeutic failure and adverse drug reactions.

Among top 10 most off-label drugs reported as per the BNF guideline, amitriptyline topped the chart with 97% off-label use out of total times prescribed. It more commonly qualifies as off-label for indication when used for headache. This is reported as unlicensed. Amitriptyline with its effect on mood profile might be effective for its use in tension-type headache.

Naproxen is the second most common drug of off-label use for its indication in headache. Trials of naproxen have proven its efficacy in headache, but it is not as efficacious as ibuprofen and sumatriptan for the same indication.^[13] BNF guidelines mention the use of aspirin in dose of 75 mg

once daily for secondary prophylaxis of stroke. There is no range specified for the use of higher doses of aspirin for secondary prophylaxis. This is in major contradiction to other guidelines including NFI also.

Out of pregabalin and gabapentin, the only two approved drugs for neuropathy as per the BNF, pregabalin reports significant off-label use in terms of dose in our study where it is prescribed in subtherapeutic dose of 75 mg, whereas minimum required dose as per the BNF is 150 mg. According to the prescribers in our tertiary care hospital, Indian population cannot tolerate initial doses of 150 mg. Hence, 75 mg is preferred dose for initiation of therapy then dose is increased as required.

Of the total 317 recorded off-label drugs in BNF, 84 drugs were referred to as unlicensed, that is, no licensed suitable alternative is available or medicine is prescribed outside the terms defined by license given by regulatory authorities. This data are only available in BNF. Unlicensed use thus highlights drug not being off-label and is yet to be approved by drug authorities. Three most common unlicensed drugs in our study are amitriptyline, atorvastatin and clonazepam. Use of atorvastatin for secondary prevention of cardiovascular events is referred to as unlicensed. Atorvastatin shows favorable effects on vasculature such as anti-inflammatory effects by inhibiting smooth muscle cell migration and proliferation, activation of macrophages, and bioaugmentation of Neutrophils.^[4] Similarly, amitriptyline is considered unlicensed for use in neuropathic pain, abdominal pain, and headache as per the BNF. However, NFI mentions use of amitriptyline in neuropathy and tension-type headache as an approved use. Use of clonazepam other than epilepsy, especially for panic disorders resistant to antidepressant therapy is considered unlicensed indication. Thus, information about unlicensed use of a drug may help the prescriber to be more sure and safe while prescribing the drug for its off-label uses.

The study uses the BNF 73rd edition (2017) and NFI 2016 in contrast to the similar study neurology which used alternate available references such as DRUGDEX system and FDA guidelines.^[4] Data of some frequently prescribed drugs such as pregabalin, duloxetine, fluvoxamine, and naproxen were missing in NFI. Moreover, data given in NFI is very much concise and misses detailed information for prescribing every drug. As compared to NFI, BNF stays regularly updated making it more preferable than NFI for studies for off-label drug use evaluation giving a better insight into the prescription pattern. BNF and NFI are being the preferred by the physicians in India as a standard desk reference.

It has been observed in our study, off-label use of certain drugs such as amitriptyline in management of headache has favored better therapeutic response among nonresponders. Similarly, use of 75 mg gabapentin in initiating therapy for neuropathy is observed to have reduced side effects and improved compliance. While off-label use does prove to be favorable, but close monitoring with repeated follow-ups also needs to be practiced. Rising aftermarket researches to explore better therapeutic options has given boost to off-label drug use among clinicians. This has also tempted pharmaceuticals to market drug for off-label use and save investments for conducting trials and approval. Off-label use is not illegal but requires monitoring and precautions to prevent adverse events following it. It should be favored only when backed by trusted scientific sources. Such information must be shared with regulatory authorities time and again to strengthen them. Strong reporting system, safe use of off-label, and proper guidelines will favor better and safe drug utilization. Limitations of this study include small sample size due to limited period of data collection, use of only two reference tools for comparison, and inability to report adverse drug reactions related to the study.

CONCLUSION

There are significant numbers of off-label drug uses prevalent in neurology outpatient unit for common neurological conditions such as epilepsy, headache, neuropathy, and stroke prophylaxis. Among the drugs prescribed, clonazepam and amitriptyline are the most commonly reported off-label drugs. "Indication" is the leading cause for drug qualifying as off-label. There is a need for raising awareness among physicians about off-label drug use and offer better compliance in prescribing medicines ensuring safer and reliable pharmacotherapy options. Formularies can serve as desk references to neurology physicians which can help improve prescribing pattern.

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Conflicts of interest

There are no conflicts of interest.

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