

ASSESSING PAKISTANI PHYSICIANS' KNOWLEDGE AND EXPERIENCE WITH OFF-LABEL USE OF MEDICINES

Original Research

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ABSTRACT

Background: Off-label prescribing, the use of pharmaceutical drugs beyond their approved indications, is a growing practice globally and raises important questions regarding safety, efficacy, and regulatory oversight. Despite its widespread application in various specialties, many healthcare providers remain unaware of the legal and ethical implications of such use. In countries like Pakistan, where formal regulations are lacking, assessing physician knowledge and behavior becomes crucial to ensure patient safety and informed clinical decision-making.

Objective: To evaluate the knowledge, attitude, and practice (KAP) of physicians in Pakistan regarding off-label drug use and identify gaps requiring policy and educational interventions.

Methods: This cross-sectional study employed a self-developed, pre-validated questionnaire distributed to 377 MBBS-qualified physicians across various hospitals in Islamabad and Rawalpindi between December 2023 and May 2024. A total of 210 valid responses were collected (response rate: 56%). The questionnaire comprised demographic data and 20 knowledge and experience-based items. Data were analyzed using SPSS version 25. Categorical variables were summarized in frequencies and percentages, and continuous variables were presented as means \pm standard deviations. Fisher's exact test and chi-square test were used to assess associations, with $p \leq 0.05$ considered statistically significant.

Results: Among the respondents, 55.7% were male and 44.3% were female; 83% were specialists and 17% were general practitioners. While 80% were familiar with the concept of off-label prescribing, only 21% correctly defined it. A total of 55.8% had prescribed off-label medications, yet 45.7% believed they had never done so, reflecting a knowledge gap. Moreover, 58% perceived off-label use as illegal, and 86.7% recommended the need for formal guidelines. Mean KAP scores were moderate across all domains, with significant differences based on gender, specialty, and experience ($p < 0.05$).

Conclusion: Physicians in Pakistan demonstrate moderate understanding and limited experience regarding off-label prescribing. The findings highlight an urgent need for regulatory frameworks and targeted education to ensure evidence-based and safe off-label drug use.

Keywords: Attitude of Health Personnel, Clinical Practice Patterns, Drug Prescriptions, Knowledge, Off-Label Use, Pakistan, Physicians.

INTRODUCTION

The approval and regulation of newly developed or discovered drugs is a rigorous process aimed at ensuring that any medicinal product entering the market demonstrates a favorable risk-benefit profile. Regulatory bodies assess both the therapeutic potential and the adverse effect profile of medications before granting authorization for specific indications, typically limited to well-defined patient groups—most commonly, adults (1). Despite these defined parameters, it is widely observed in clinical practice that drugs are often prescribed in ways that deviate from their approved indications, dosing regimens, or target populations, a practice termed as "off-label use" (2). According to the World Health Organization (WHO), nearly half of all approved medicines are used for indications not included in their labeling (3,4). Off-label drug use involves prescribing medications in a manner not specified in the approved summary of product characteristics (SPC), and it has become an increasingly prevalent phenomenon across various medical specialties (5). Alarming, a considerable proportion of these off-label prescriptions are issued without strong or sufficient supporting evidence. One study highlighted that 21% of 160 commonly used drugs were prescribed off-label, with most lacking high-quality clinical support for their alternate use (6). A similar pattern was observed across major therapeutic drug classes, with approximately three drugs per class being used off-label, accounting for 21% of total usage (7,8).

The regulatory landscape for off-label prescribing is inconsistent worldwide, reflecting varied ethical, legal, and clinical perspectives. In certain scenarios—such as during pandemics, treatment-resistant conditions, or when dealing with complex diseases like cancer—off-label prescribing may offer vital therapeutic options, albeit with significant risks (9). For instance, Spain restricts such practices to exceptional cases and mandates informed consent, while the United Kingdom has well-outlined guidelines issued by the General Medical Council to safeguard patient well-being (10). On the contrary, India prohibits off-label prescriptions altogether, whereas Pakistan lacks specific regulatory directives on this matter. Physicians in Pakistan often rely on a combination of Food and Drug Administration (FDA) guidance and European Union regulations, especially those related to pediatric drug use (11,12). Nonetheless, the legal and ethical obligation remains for clinicians to inform patients about the off-label nature of such treatments and the potential associated risks (13). Emerging evidence further raises concerns regarding patient safety, as studies have linked off-label drug use to a significantly higher incidence of adverse events. A recent analysis indicated a 44% increase in adverse drug reactions associated with off-label prescriptions (14). This can be attributed to the frequent lack of robust clinical data supporting such uses, leading to unpredictable outcomes and undermining patient safety (15). Given the increasing reliance on off-label prescribing and the notable absence of national guidelines in Pakistan, there is a critical need to explore how physicians perceive and engage in this practice. The current study aims to investigate the knowledge, attitudes, and practices of Pakistani physicians regarding off-label medication use, with the objective of identifying gaps in awareness and highlighting potential risks associated with unregulated prescribing behaviors.

METHODS

This study employed an empirical, illustrative, and cross-sectional design to evaluate the knowledge, attitudes, and practices of physicians regarding off-label drug use. A prospective, questionnaire-based survey was conducted over a six-month period between December 2023 and May 2024 in the twin cities of Pakistan, namely Islamabad and Rawalpindi. The target population comprised practicing physicians holding an MBBS qualification and currently working in public and private hospitals across various clinical specialties. Allied health professionals such as physiotherapists, nutritionists, and house officers were excluded to ensure the sample strictly reflected licensed medical practitioners with prescribing authority. The sample size was estimated using Raosoft®, an online sample size calculator, which recommended a minimum of 377 participants for a 95% confidence level and a 5% margin of error. Consequently, 377 questionnaires were distributed, and responses were collected from 300 physicians, resulting in a response rate of approximately 79.6%. Prior to the main survey, a pilot study was conducted involving thirty expert physicians to validate the clarity, relevance, and internal consistency of the questionnaire. This ensured that all survey items were understandable, clinically relevant, and contextually appropriate.

Data were gathered using a self-developed, pre-validated structured questionnaire composed of three sections. The first section collected demographic and professional characteristics, including age, gender, years of clinical experience, and the age group of patients

commonly treated. The second section assessed knowledge about off-label prescribing through 10 close-ended questions. The third section focused on physicians' practical experiences with off-label drug use and consisted of 10 items exploring prescribing habits, perceived outcomes, and commonly used off-label medications. A variety of question formats were used, including binary (Yes/No), multiple-choice, and two open-ended items to allow for more nuanced responses. Informed consent was obtained from all participants prior to their involvement in the study, and the ethical protocol was reviewed and approved by the Research Ethics Committee (REC) of the University. All procedures were conducted in accordance with the Declaration of Helsinki, ensuring participant anonymity, voluntary participation, and data confidentiality. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Descriptive statistics were used to summarize demographic data and survey responses. Frequencies and percentages were calculated for categorical variables, whereas means and measures of variance (standard deviation) were computed for continuous variables. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Fisher's exact test was applied to evaluate associations between categorical variables, and a p -value ≤ 0.05 was considered statistically significant.

RESULTS

Out of 377 distributed questionnaires, 210 were completed appropriately, yielding a response rate of 56%. Of the respondents, 55.7% were male and 44.3% were female. Most participants (83%) were specialists, while the remaining were general practitioners. The majority of respondents reported being reasonably or very familiar with the concept of off-label prescribing. A statistically significant association was observed between physicians' specialty and their familiarity with off-label use ($p=0.034$), as well as with their understanding of its definition ($p=0.007$) and perceived outcomes of such prescriptions ($p=0.007$). Regarding information sources used during off-label prescribing, 21% of participants referred to the British National Formulary, while others cited national guidelines, local formularies, and clinical databases such as PubMed and Medscape. Approximately 50% of participants believed that off-label prescribing compromises prescription appropriateness, and a similar proportion expressed concern that the available risk-benefit data are insufficient. Notably, 72.2% of GPs and 80.5% of specialists expressed concerns about the efficacy of off-label medications. Physicians reported encountering practical challenges related to off-label prescribing, including refusal of funding, patient and pharmacist skepticism, and institutional sanctions. A majority cited unavailability of alternative treatments, economic constraints, and the prohibitive cost and time of new drug development as key reasons for resorting to off-label options. Furthermore, 58% of respondents believed off-label prescribing is not legal in Pakistan, and 90% advocated for clear regulatory guidance.

A statistically significant association was found between physician specialty and the perceived risks associated with off-label use ($p=0.005$). The association between specialty and previous experiences with off-label drug outcomes was also significant ($p=0.007$). The majority (65%) of physicians expressed willingness to participate in clinical trials investigating off-label uses. Bivariate analysis revealed a mean knowledge score of 64.03 ± 26.7 , an attitude score of 5.91 ± 2.12 , and a practice score of 25.23 ± 7.6 . Male physicians demonstrated significantly higher scores than females in all three domains: knowledge (69.48 vs 57.17 , $p=0.079$), attitude (6.26 vs 5.4 , $p=0.019$), and practice (26.35 vs 23.81 , $p=0.009$). Physicians with more than five years of experience had higher knowledge scores (78.21) compared to those with less experience (61.09), with increasing age also correlating with improved scores in all domains. Practice scores remained relatively consistent across age and experience categories but were highest among physicians aged 36–45 years (mean score 26.87). Knowledge scores varied significantly by specialty, with pulmonology (90.3), dermatology (79.7), and oncology (80.5) showing the highest mean scores. Attitude and practice scores showed less variation across specialties. The chi-square test demonstrated significant associations between gender and knowledge ($p=0.079$), attitude ($p=0.019$), and practice scores ($p=0.009$). Years of clinical experience had a significant effect on practice scores ($p=0.001$) but not on knowledge or attitude. No statistically significant differences in KAP scores were noted across different patient age groups.

Based on further analysis, the study assessed the association between Knowledge, Attitude, and Practice (KAP) scores and clinical outcomes such as adverse drug reactions (ADRs), treatment failure, and whether off-label drug use met physicians' expectations. Physicians with higher knowledge scores (≥ 65) reported fewer ADRs (30% vs 40%), lower treatment failure rates (20% vs 34%), and more consistent alignment of results with clinical expectations (65% vs 45%) compared to those with lower knowledge levels. Similar trends were observed across attitude and practice domains, where higher scores were associated with more favorable clinical outcomes. These findings suggest a positive correlation between stronger KAP scores and patient safety outcomes, reinforcing the need for improved physician education regarding off-label practices. Subgroup analysis by specialty revealed that pulmonologists, dermatologists, and oncologists achieved the highest mean knowledge scores (90.3 , 79.7 , and 80.5 respectively), and also demonstrated high practice and attitude scores. However, specialties such as gastroenterology and psychiatry, despite high practice or attitude scores,

reported elevated ADR rates (42% and 40% respectively), indicating potential variability in outcome regardless of KAP alignment. This suggests that specialty-specific dynamics and clinical complexity may influence off-label prescribing outcomes beyond KAP measures alone. These findings highlight the necessity of tailored regulatory oversight and continuing education programs specific to different medical specialties to mitigate patient safety risks.

Table 1: Response to the Questions of the Study

S.No.	Question	Answer Options	GP (n=36)	GP (%)	Specialty (n=174)	Specialty (%)	p- value
1	Familiarity with off-label prescribing	Very familiar	4	11.1%	54	31.0%	0.034
		Reasonably familiar	26	72.2%	91	52.3%	
		Unfamiliar	6	16.6%	29	16.7%	
2	Most appropriate definition of off-label use	Auth. med. used for other than FDA indication	22	61.1%	75	43.1%	0.007
		Non-auth. med. for human use	2	5.5%	39	22.4%	
		Auth. med. used not by the label	11	30.5%	35	20.1%	
		Auth. med. used in unapproved subpops	1	2.7%	25	14.4%	
3	Information sources used	British National Formulary	4	11.1%	22	12.6%	0.640
		Local formulary	3	8.34%	30	17.24%	
		National guidelines	7	19.45%	25	14.9%	
		Summary of product characteristics	7	19.45%	26	14.9%	
		Medscape	3	8.34%	10	5.7%	
		NCCN guidelines	4	11.1%	13	5.7%	
		PubMed	2	5.5%	3	1.7%	
		Up to date	0	0%	4	2.3%	
		Personal knowledge	0	0%	3	1.7%	
4	Negative impact on prescription appropriateness	None	6	16.6%	38	21.8%	0.669
		Much	11	30.5%	69	40%	
		Not much	11	30.5%	47	27%	
		Often	7	19.45%	34	19.5%	
5	Access to sufficient scientific info	Rarely	7	19.45%	24	13.8%	0.145
		No	22	61.2%	82	47.1%	
6	Risk/benefit ratio is appropriate	Yes	14	38.8%	92	52.9%	0.497
		No	18	50%	90	51.7%	
7	Need for clear rules & regulations	Yes	18	50%	84	48.2%	0.178
		No	7	19.45%	21	12.0%	
8	Off-label prescribing is widespread in Pakistan	Yes	29	80.55%	153	88%	0.374
		No	12	33.34%	66	38%	
9	Pakistan legislation allows off-label use	Yes	24	66.67%	108	62%	0.392
		No	22	61.2%	99	57%	
10	Ever prescribed a medicine off-label	Yes	14	38.8%	75	43%	0.226
		No	19	52.78%	77	44.2%	
11	Inform patients before off-label prescribing	Yes	17	47.23%	97	55.8%	0.339
		No	15	41.67%	50	28.7%	
		Yes	15	41.67%	86	49.4%	
12		None	6	16.6%	38	21.8%	0.187
		No	10	27.78%	34	19.5%	

S.No.	Question	Answer Options	GP (n=36)	GP (%)	Specialty (n=174)	Specialty (%)	p- value
	Concerns about efficacy of off-label medicines	Yes	26	72.2%	140	80.5%	
13	Frequency of off-label prescribing	Sometimes	10	27.78%	43	24.7%	0.268
		Often	3	8.34%	25	14.9%	
		Very often	1	2.7%	20	11.4%	
		Rarely	16	44.45%	48	27.5%	
		Never	6	16.6%	38	21.8%	
14	Prescribed off-label and approved drugs for same indication	No	27	75%	102	58.6%	0.090
		Yes	9	25%	72	41.4%	
15	Reasons for off-label prescribing	Age	6	16.6%	21	12.0%	0.757
		Indication	12	33.34%	54	31.3%	
		Dosage	1	2.7%	21	12%	
		Formulation	2	5.5%	11	6.3%	
		Route of administration	1	2.7%	10	5.7%	
		Cost	3	8.34%	10	5.7%	
		Availability	0	0%	4	2.3%	
		Lack of treatment options	1	2.7%	4	2.3%	
		None	10	27.78%	39	22.4%	
16	Off-label results as expected	Sometimes	8	22.23%	32	18.3%	0.007
		Often	7	19.45%	54	31%	
		Very often	1	2.7%	25	14.3%	
		Rarely	6	16.6%	15	8.6%	
		Never	8	22.23%	10	5.7%	
		None	6	16.6%	38	21.8%	
17	Experienced treatment failure due to off-label use	Sometimes	9	25%	33	19%	0.338
		Often	3	8.34%	25	14.3%	
		Very often	3	8.34%	26	14.9%	
		Rarely	6	16.6%	31	17.8%	
		Never	9	25%	21	12%	
		None	6	16.6%	38	21.8%	
18	Reasonable reasons for off-label use	Lack of alternative treatment	10	27.78%	50	28.7%	0.843
		New data/evidence	8	22.23%	31	17.8%	
		Personal experience	5	13.89%	31	17.8%	
		Economic reasons	3	8.34%	23	13.2%	
		None	10	27.78%	39	22.4%	
19	Risks related to off-label use	Adverse reactions	13	36.12%	33	19%	0.005
		Improper formulation	0	0%	35	20.1%	
		Inefficiency	7	19.45%	42	24.1%	
		Increase in therapeutic error	6	16.6%	25	14.3%	
		None	10	27.78%	39	22.4%	
20	Patients experienced ADR from off-label medicine	No	19	52.78%	70	40.2%	0.406
		Yes	11	30.5%	65	37.3%	
		None	6	16.6%	39	22.4%	
21	Willing to join clinical trials on off-label use	No	15	41.6%	61	35%	0.258
		Yes	21	58.3%	113	65%	

Table 2: Mean Knowledge, Attitude, and Practice (KAP) Scores

Variable	Knowledge (Mean ± SD)	Attitude (Mean ± SD)	Practice (Mean ± SD)	p-value (Knowledge)	p-value (Attitude)	p-value (Practice)
Gender						
Male	69.48 ± 28.23	6.26 ± 2.2	26.35 ± 8.5	0.079	0.019	0.009
Female	57.17 ± 23.22	5.4 ± 6.06	23.81 ± 6.06			
Experience						
< 5 years	61.09 ± 24.7	5.05 ± 2.08	23.5 ± 6.7	0.188	0.256	0.001
5 – 10 years	65.31 ± 29.69	6.29 ± 2.17	26.7 ± 7.9			
11 – 15 years	63.34 ± 28.44	6.10 ± 2.05	26.27 ± 8.0			
> 15 years	78.21 ± 16.24	6.2 ± 1.8	26.0 ± 9.6			
Age (Years)						
25 – 35	59.89 ± 24.74	5.5 ± 2.09	24.1 ± 6.7	0.345	0.171	0.001
36 – 45	67.65 ± 29.56	6.3 ± 2.2	26.87 ± 8.3			
46 – 55	69.33 ± 28.79	6.1 ± 2.0	25.14 ± 8.66			
> 55	74.11 ± 15.94	6.0 ± 1.5	25.67 ± 9.05			
Patient Age Group						
0 – 15 years	61.5 ± 30.61	5.8 ± 2.3	25.02 ± 8.4	0.92	0.714	0.824
15 – 40 years	63.08 ± 26.85	6.0 ± 2.07	25.63 ± 7.4			
Above 40 years	68.73 ± 23.50	5.7 ± 2.06	24.34 ± 7.6			
Specialty						
Oncology	80.5 ± 10.17	6.0 ± 1.8	24.5 ± 7.8	0.001	0.194	0.432
Cardiology	77.6 ± 14.61	5.6 ± 2.5	28.7 ± 7.5			
Dermatology	79.7 ± 17.11	6.6 ± 1.9	27.2 ± 8.5			
Pediatric	71.9 ± 29.01	5.3 ± 2.2	23.7 ± 8.1			
Pulmonology	90.3 ± 7.3	5.5 ± 2.9	25.0 ± 9.8			
Psychiatry	51.1 ± 31.8	6.3 ± 2.3	27.0 ± 8.6			
Medicine	61.3 ± 23.3	5.6 ± 2.21	25.06 ± 7.6			
Gynecology	53.2 ± 17.5	5.8 ± 1.71	24.03 ± 5.51			
Surgery	66.41 ± 31.29	6.3 ± 2.2	23.16 ± 10.2			
Orthopedics	56.90 ± 28.04	5.7 ± 2.4	24.5 ± 9.5			
Neurology	57.17 ± 32.06	6.4 ± 1.9	24.65 ± 6.3			
Gastroenterology	49.3 ± 39.01	6.6 ± 2.3	29.0 ± 7.8			
Nephrology	52.09 ± 12.20	6.1 ± 2.3	26.8 ± 7.6			
General Practice	68.08 ± 19.4	5.5 ± 2.1	25.3 ± 7.6			

Table 3: KAP Scores vs Clinical Outcomes

Variable	ADR (%)	Treatment Failure (%)	Expected Results (%)
Knowledge			
High Knowledge (≥65)	30	20	65
Low Knowledge (<65)	40	34	45
Attitude			
High Attitude (≥6)	28	22	68
Low Attitude (<6)	38	33	47
Practice			
High Practice (≥26)	25	21	70
Low Practice (<26)	42	35	43

Table 4: Subgroup Specialty Analysis (KAP & ADR Experience)

Specialty	Knowledge Score	Attitude Score	Practice Score	ADR (%)
Pulmonology	90.3	5.5	25.0	35
Dermatology	79.7	6.6	27.2	20
Oncology	80.5	6.0	24.5	18
Psychiatry	51.1	6.3	27.0	40
Gastroenterology	49.3	6.6	29.0	42
General Practice (GP)	68.08	5.5	25.3	37

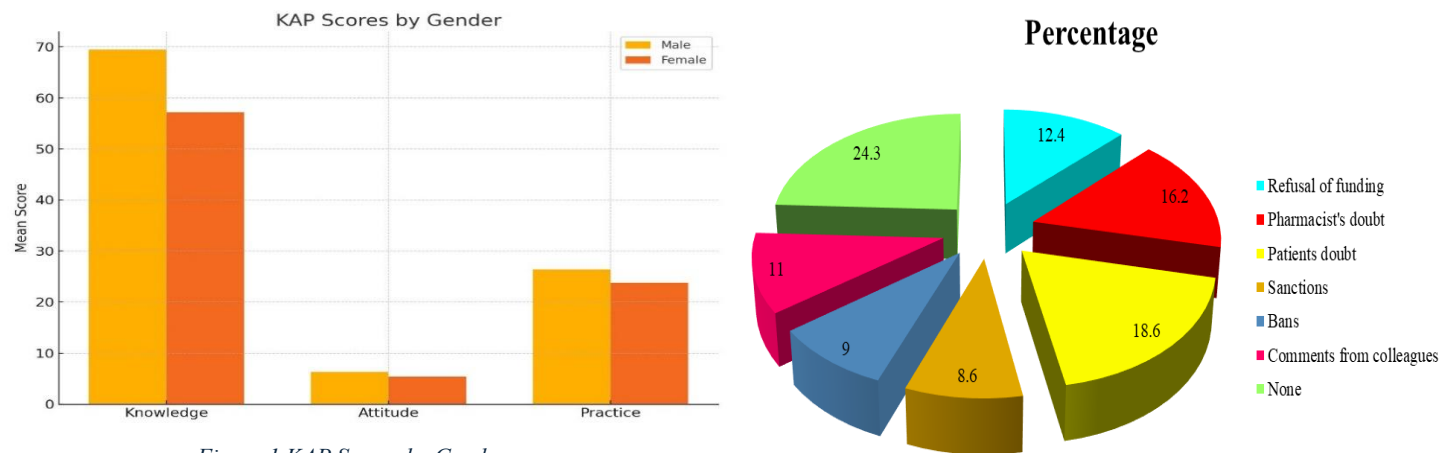


Figure 1 KAP Scores by Gender

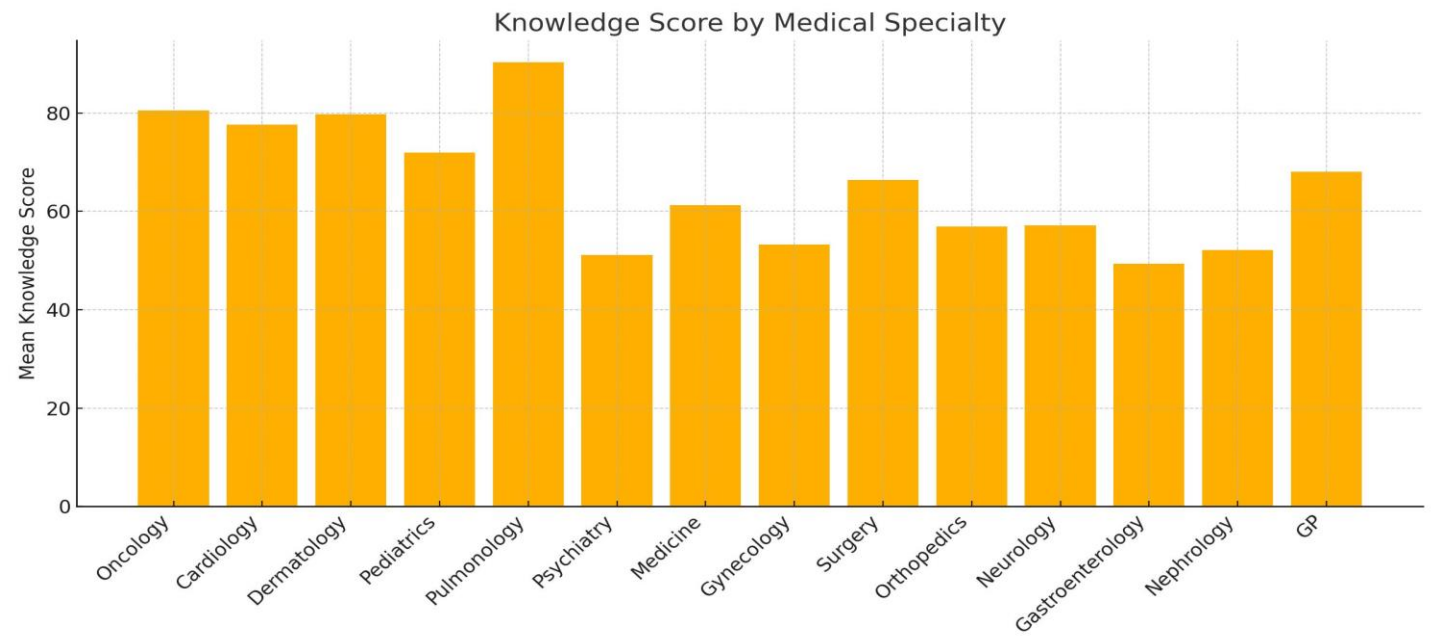
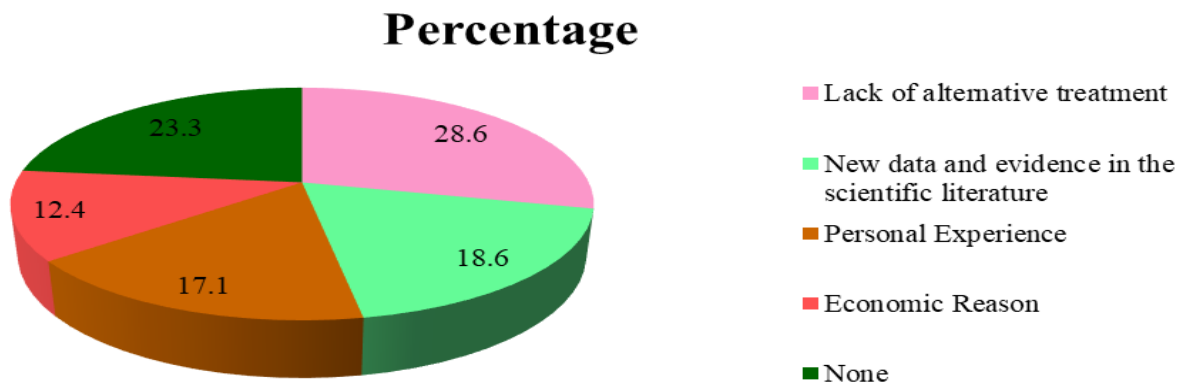


Figure 2 Knowledge Score by Medical Specialty



DISCUSSION

The findings of this study underscore the widespread prevalence of off-label prescribing among physicians in Pakistan, particularly within urban clinical settings. The notable rise in off-label use across various specialties reflects a broader global trend, where modern research data and emerging therapeutic needs have driven clinicians to adopt novel treatment approaches beyond regulatory indications (16). Approximately 80% of surveyed physicians demonstrated awareness of the concept of off-label prescribing, a finding that aligns closely with earlier surveys conducted within the European Union, highlighting a parallel in baseline knowledge levels across international contexts (17). However, the depth of this knowledge remains questionable, as only 21% of participants correctly identified the regulatory definition—emphasizing the use of an approved medication beyond its labeled indication—which suggests a considerable gap in foundational understanding despite surface-level familiarity. The study revealed that a significant proportion of physicians, although engaged in off-label prescribing, did not recognize their practices as such. This reflects a concerning lack of clarity about regulatory boundaries and points toward an implicit normalization of off-label usage in clinical practice. In contrast, previous surveys, such as one conducted in Bulgaria, reported a lower self-reported prevalence of off-label prescribing (18,19), likely due to exclusion of non-respondents and differing interpretations of off-label criteria. In this study, 45.7% of respondents stated they had never prescribed an off-label drug, yet further responses suggest discrepancies between perception and actual practice.

Off-label use was not confined to a particular drug category, with medications like metformin (5.7%), amitriptyline, rifaximin, misoprostol, and clonazepam frequently mentioned, echoing patterns observed in prior research (20,21). This raises particular concern in fields such as female reproductive health and pediatrics, where a high proportion of medications are prescribed without formal approval for the targeted age group or indication. Pediatric off-label use was especially highlighted as a significant ethical and clinical concern, primarily due to the lack of pediatric formulations and inadequate clinical trial representation for children (22,23). Interestingly, this study diverged from previous literature by indicating a higher prevalence of off-label prescribing in adult patients compared to children. Legal ambiguity was also a central theme. Approximately half of the participants believed off-label prescribing is permitted under Pakistani legislation, while the other half considered it unauthorized. Existing literature confirms the absence of definitive laws or formalized national guidelines in Pakistan regarding off-label drug use (24). This legal vacuum contributes to inconsistency in clinical decision-making and underscores the urgent need for national regulatory bodies to develop structured, evidence-based frameworks. A large majority (87%) of physicians advocated for the establishment of clear guidelines to mitigate uncertainty and promote patient safety, mirroring concerns raised in European and South Asian contexts (25).

The study further emphasized that access to reliable scientific information remains limited, with half of the participants expressing dissatisfaction regarding available evidence to support off-label decisions. This reinforces the findings of international studies, which have reported similar concerns about the lack of centralized resources and structured data repositories for guiding off-label prescribing (24,25). In such an environment, clinical decision-making may be influenced more by anecdotal experience or peer recommendations than by validated clinical evidence. Among the strengths of this study is its timely focus on a critical and under-researched area within the Pakistani healthcare system. It employed a validated, structured questionnaire and incorporated a pilot study to refine data collection. The statistical correlation between knowledge, attitude, and practice with patient safety outcomes further enhances the credibility of its conclusions. However, several limitations must be acknowledged. The sample was geographically restricted to the twin cities of

Pakistan, potentially limiting generalizability to rural or less-resourced areas. Moreover, the study relied on self-reported data, which may be prone to response bias, especially considering the sensitive nature of prescribing practices that fall outside approved norms.

Future research should aim to include a more diverse geographical sample encompassing rural and underdeveloped regions of the country to gain a comprehensive national perspective. Additionally, qualitative interviews could complement survey-based methods to explore deeper insights into physicians' decision-making processes, ethical dilemmas, and the institutional pressures that influence off-label use. Longitudinal studies assessing patient outcomes directly linked to off-label prescribing are also warranted to establish more robust evidence on the risks and benefits of such practices in the local context. In conclusion, while off-label prescribing offers clinicians flexibility in therapeutic decision-making, the findings of this study reveal critical gaps in physician knowledge, regulatory guidance, and access to scientific resources. Addressing these challenges through clear policy development, continuous medical education, and improved pharmacovigilance systems is essential to safeguard patient welfare and promote responsible prescribing in Pakistan.

CONCLUSION

This study concludes that while off-label drug prescribing is a common practice among physicians, particularly general practitioners, there remains a moderate level of knowledge and awareness regarding its appropriate use. Concerns related to the efficacy and safety of such prescriptions highlight the pressing need for structured national guidelines and regulatory oversight. Aligning with practices observed in other healthcare systems, especially within the European Union, the establishment of clear rules and comprehensive educational programs would support more informed clinical decisions and protect patient welfare. The findings emphasize the importance of strengthening both policy and professional training to ensure responsible, evidence-based off-label prescribing across all medical disciplines in Pakistan.

AUTHOR CONTRIBUTION

Author	Contribution
Nimra Ansar	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Areej Mumtaz	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Laiba Asad	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Najam-us-Sahar	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ayesha Sana*	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Kashif Iqbal	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

REFERENCES

1. Svitlana, D., Kateryna, K., Tsyvunin, V., Viktoriia, H., Anatolij, L., Olexandr, V., & Dmitriy, Z. Positive and negative aspects of the off-label drugs use. *Pharmacologyonline*. 2021; 2:1179-85.
2. Shakeel, S., Iffat, W., Qamar, A., Nesar, S., Butt, F., Siddiqui, S. N., & Rehman, H. Assessment of Knowledge, Attitude, and Practice of Obstetricians and Gynecologists Toward Off-Label Medicine Use in Female Reproductive Health Issues. *Front. Public Health*. 2022 Mar 24; 10:829339.
3. Shakeel, S., Hassali, M. A., Rehman, H., Rehman, A. U., & Muneswarao, J. Knowledge, attitude, and practice towards biosimilars and interchangeable products: a prescriptive insight by the pharmacists. *Int. J. Gen. Med*. 2020; 1075-1082.

4. Husaini DC, Abubakar Y, Mphuthi DD. Stockpiling on off-label medicines in preparation for COVID-19 in Belize: a qualitative study. *Int. J. Med. Sci.* 2021. 26;8.
5. Shakeel S, Nesar S, Rehman H, Jamil K, Mallick IA, Mustafa MS, Anwar M, Jamshed S. Patterns and predictors of off-label drug prescribing in psychiatric practice: a qualitative study. *Pharmacy.* 2021 ;9(4):203.
6. Drenska M, Naseva E, Getov I. Physician's knowledge and experience with the off-label use of medicines. *Biotechnol. Biotechnol. Equip.* 2021 ;35(1):111-6.
7. Radojević S, Krajnović D. Use of off-label medicines in the pediatric population. *TMG.* 2021;46(2):86-92.
8. Onavbavba G, Alemede VO, Uzu IF. Off-Label Use of Medicines in Children Attending a Secondary Healthcare Facility in Federal Capital Territory. *J. Med. Health.* 2021;173.
9. Shah, H.P., et al., *Assessing National Trends and Perceived Safety of Off-Label Ciprofloxacin-Dexamethasone Use by Pediatric Otolaryngologists.* *Laryngoscope*, 2024. **134**(6): p. 2922-2930.
10. Drapkina, O.M., et al., *Assessment of Awareness and Experience of Using off-label Drugs by Doctors of Clinical Specialties.* *Kardiologiya*, 2021. **61**(5): p. 41-50.
11. Shakeel, S., et al., *Assessment of Knowledge, Attitude, and Practice of Obstetricians and Gynecologists Toward Off-Label Medicine Use in Female Reproductive Health Issues.* *Front Public Health*, 2022. **10**: p. 829339.
12. De Bondt, E., et al., *Awareness of national dementia guidelines and management of oldest-old and frail people living with dementia: a European survey of geriatricians.* *Eur Geriatr Med*, 2025. **16**(2): p. 527-539.
13. McKibbin, R., *The effect of RCTs on drug demand: Evidence from off-label cancer drugs.* *J Health Econ*, 2023. **90**: p. 102779.
14. Meng, M., et al., *Guideline for the management of pediatric off-label use of drugs in China (2021).* *BMC Pediatr*, 2022. **22**(1): p. 442.
15. Chansky, M.C., et al., *Influence of data disclosures on physician decisions about off-label uses: findings from a qualitative study.* *BMC Prim Care*, 2022. **23**(1): p. 87.
16. Weldon, E., et al., *Medical Malpractice Litigation Due to Off-Label Use of Bone Morphogenetic Protein.* *Spine (Phila Pa 1976)*, 2023. **48**(22): p. 1575-1580.
17. Andersen, N.M., et al., *Medical practitioners' experiences and considerations when managing sleep medication for adolescents and young adults.* *Scand J Prim Health Care*, 2025. **43**(1): p. 120-130.
18. Rusz, C.M., et al., *Off-Label Medication: From a Simple Concept to Complex Practical Aspects.* *Int J Environ Res Public Health*, 2021. **18**(19).
19. van Hoorn, C.E., et al., *Off-label use of dexmedetomidine in paediatric anaesthesiology: an international survey of 791 (paediatric) anaesthesiologists.* *Eur J Clin Pharmacol*, 2021. **77**(4): p. 625-635.
20. Müller, L., et al., *Off-label use of quetiapine in nursing homes: Does medical specialty of prescribing physicians play a role?* *Br J Clin Pharmacol*, 2020. **86**(7): p. 1444-1445.
21. Ebm, C., et al., *Potential harm caused by physicians' a-priori beliefs in the clinical effectiveness of hydroxychloroquine and its impact on clinical and economic outcome - A simulation approach.* *J Crit Care*, 2021. **62**: p. 138-144.
22. Han, S.H., et al., *Practice Patterns and Perspectives of the Off-Label Use of GLP-1 Agonists for Cosmetic Weight Loss.* *Aesthet Surg J*, 2024. **44**(4): p. Np279-np306.
23. Drabiak, K., *The Problem with Using Medical Boards to Regulate Misinformation.* *J Leg Med*, 2023. **43**(1-2): p. 3-18.
24. Okuyama, E., et al., *Radiologist expertise and responsibilities for off-label use of Urografin before the change in indication by medical health insurance.* *Jpn J Radiol*, 2023. **41**(8): p. 909-910.
25. van der Zanden, T.M., L. Schrier, and S.N. de Wildt, *[A step-by-step guide for safe off-label prescribing].* *Ned Tijdschr Geneesk*, 2021. **165**.