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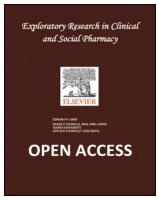

Exploration of drug therapy related problems in a general medicine ward of a tertiary care hospital of Eastern Nepal

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ABSTRACT

Background: Inpatients are at higher risk of Drug Therapy Related Problems (DTRPs), and early identification and management of these DTRPs is crucial for optimal treatment outcomes and ensuring rational drug therapy.
Objective: This study aims to assess DTRPs in a general medicine ward of a tertiary care hospital in eastern Nepal.
Methods: A three-month prospective observational study was conducted on inpatients admitted to the general medicine ward of the hospital. Pharmacists routinely performed patient drug therapy reviews, by which suspected DTRPs were identified and recorded as per the Pharmaceutical Care Network Europe Association (PCNE) v.9.1 guidelines. Binary logistic regression analysis was used to determine the influence of predictor variables on the occurrence of DTRPs.
Results: A total of 301 inpatients were enrolled, out of which 233 (77.4%) had one or more DTRPs. Altogether, 528 DTRPs with an average of 2.27 ± 0.92 DTRPs per patient were identified. The primary causes of the DTRPs were drug selection (40.47%), treatment duration (16.71%), dispensing (15.75%), and dose selection (13.12%). Antimicrobials were involved in 55.18% of the DTRPs. DTRPs were more prevalent in elderly, comorbid patients, patients with longer hospital stay days, and polypharmacy, which was statistically significant ($p<0.05$). Furthermore, multivariate binary logistic regression analysis showed that geriatric patients had a higher risk of experiencing DTRPs, with an adjusted odds ratio of 1.832 (1.021-3.286) at p-value < 0.05.
Conclusion: DTRPs are frequently prevalent in hospital wards, emphasizing the crucial role of clinical pharmacists in identifying, resolving, and preventing DTRPs in inpatient settings for optimal treatment outcomes.

1. Introduction

Drugs play a crucial role in preventing, treating, and curing diseases; however, they are not without risks. While medications are typically prescribed when their benefits outweigh potential risks,[1] the improper use of drugs can significantly increase the likelihood of Drug Therapy Related Problems (DTRPs), leading to treatment failure and possible harm to patients.[2] According to the Pharmaceutical Care Network Europe (PCNE), "A Drug Therapy Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".[3] These problems can occur at any stage of the healthcare process, but mostly in the prescribing, dispensing, and administration phases, posing serious safety risks for patients.[4,5]

Patients admitted to medical wards are especially susceptible to DTRPs due to factors such as frequent changes in treatment regimens, polypharmacy, advanced age, chronic comorbidities, and extended hospital stays.[5] Previous studies conducted in different countries have shown significant variations in the prevalence of DTRPs among medical ward patients, with rates ranging from 15.5% in Thailand[6] to 80% in Turkey.[7] Many studies report high numbers of DTRPs per patient, emphasizing the critical nature of the issue. For example, research in Switzerland[8] and Norway[9] found that patients experienced an average of 2.6 and 2.1 DTRPs, respectively, while elderly patients in England[10] reported up to 5.9 DTRPs per patient. The consequences of DTRPs are far-reaching, leading to extended hospital stays, increased healthcare costs, reduced quality of life, and, in severe cases, higher risks of morbidity and mortality.[2] Efforts to improve medication therapy

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and prevent DTRPs can significantly enhance patient outcomes, reduce healthcare expenditures, and improve quality of life.[11]

Several classification systems, including the American Society of Hospital Pharmacists (ASHP) classification, Cipolle/Morley/Strand, Granada consensus, Hanlon approach, Hepler-Strand, Krska et al., and Mackie classification, have been developed over the years to identify and categorize DTRPs.[2] However, they lacked the comprehensiveness of PCNE, potentially leading to underreporting of DRPs.[12] The Pharmaceutical Care Network Europe Association (PCNE) system classification is structured, validated, continuously tested, and includes comprehensive domains for problems, causes, interventions, and outcomes, making it an effective tool for micro-analyzing and tracking DTRPs in detail.[3,13] Despite some limitations, such as its inability to assess the severity and preventability of DTRPs, PCNE is the classification system that comes closest to meeting the ideal requirements for a DTRPs classification system.[13] Overall, this system is essential for identifying and resolving DTRPs, providing a comprehensive, structured process that enables pharmacists to contribute to positive patient outcomes effectively.[5]

Drug Therapy Related Problems (DTRPs) can interfere with achieving optimal patient outcomes. Fortunately, a considerable proportion of DTRPs can be prevented, and clinical pharmacists (CPs) can contribute to rational drug use by identifying and managing DTRPs.[5,8,11] Pharmacists play a critical role in multidisciplinary teams, especially in medical wards, where their involvement has been linked to improved patient outcomes by effectively identifying and resolving drug therapy-related problems.[11,8] Nepal's prescribing patterns face several challenges, including low compliance with WHO prescribing indicators, high prescription errors, over-prescription, and underutilization of generic medicines.[14] Numerous studies have highlighted these issues, with a particular emphasis on the overuse of antibiotics. For instance, research by Basnet et al.[15] and Koirala et al.[16] documented the excessive use of antibiotics, the frequent prescription of branded antibiotics, the use of antibiotics not included in the essential medicines list, prophylactic antibiotic use, and the empirical treatment of suspected infections without pathogen isolation. These prescribing trends indicate a higher prevalence of drug DTRPs in Nepal.

As per the Hospital Pharmacy Guidelines 2072, hospitals with over 100 beds must employ at least one clinical pharmacist, three pharmacists, and six assistant pharmacists to ensure efficient pharmacy services.[17] However, these guidelines remain largely unimplemented, even in government hospitals, and clinical pharmacy practices in Nepal are still insufficiently deployed in inpatient settings,[18,19] so assessing the prevalence of Drug Therapy Related Problems (DTRPs) among inpatients in such settings is imperative. A previous study conducted in the critical care unit of a major urban hospital revealed a substantial prevalence of DTRPs (74.2%).[20] Although numerous studies have been conducted worldwide to assess DTRPs, very few have been carried out in Nepal. This has impeded health professionals and authorities from effectively depicting the existing and potential DTRPs occurring in inpatient settings and comprehending the significant role of adopting pharmaceutical care services in hospitals in Nepal. Therefore, this study is intended to assess drug-related problems using PNCE guidelines for the first time in a general medicine ward of a tertiary care government hospital in Eastern Nepal.

2. Method

2.1. Ethics approval

The ethical approval was obtained from the Purbanchal University School of Health Sciences- Institutional Review Committee (PUSHS-IRC Ref.no.: 031-080/81). Approval for the data collection from the hospital was obtained from the Hospital board (Koshi Hospital Ref. No. 2196). Participation was voluntary, and written informed consent was obtained from the patient or legally authorized representative (Caregiver) before data collection.

2.2. Study design, sample size, and selection criteria

A prospective observational study was conducted at the General Medicine Ward of Koshi Hospital, Biratnagar, Nepal, from January 2024 to April 2024. Koshi Hospital, a government-run tertiary care facility, has 350 beds and offers specialized services in Medicine, Pediatrics, Psychiatry, Radiology, Dermatology, and more, treating approximately 1,000 to 1,200 patients daily across all departments.[21] To calculate the sample size for the study, we used a prevalence-based estimate calculator, aiming for a 95% confidence interval and a 5% margin of error.[22] The estimated sample size was 278, considering a 23% prevalence of DRPs based on previous studies.[23] A consecutive sampling technique was used in the eligible patients to select the participants for the study. All hospitalized inpatients of either sex of any age who provided consent, stayed in the hospital ward bed for more than 24 hours, received a confirmed diagnosis, and undergoing medical treatment were included in the study. Patients who refused to participate, had an unconfirmed diagnosis, died, were transferred, left against medical advice, or were treated for less than one day were excluded from the study. Out of 479 patients admitted during the study period, only 301 patients fulfilled the inclusion criteria and were included in the final analysis.

2.3. Identification and categorization of DTRPs

Pharmacists routinely performed drug therapy reviews of the participants enrolled in the study on a daily basis upon coordination with a physician, from admission to discharge. All relevant information was collected in a specifically designed patient profile form and data collection form based on the PCNE v.9.1 categorization systems. Information related to patients' demographic characteristics, chief complaints, patients' medical and medication history, details of laboratory investigation, diagnosis, medication chart records, and follow-up updates were noted and updated in individual patients' profile forms on a daily basis, and any suspected DTRPs during the period were classified and recorded in data collection form of PCNE v.9.1 categorization systems. Patient case files, physician notes, nursing cardex, medication charts, clinical laboratory reports, and patient interviews were the sources of all pertinent data. Drug Therapy Related Problems were assessed following the Problem and Cause domain of the PCNE Classification v.9.1, based on evidence sources. Whenever a cause was identified, the corresponding potential problems were also noted. Therefore, the study included both potential and actual problems according to PCNE v.9.1.

The British National Formulary 85,[24] National Antimicrobial Treatment Guidelines 2023,[25] Micromedex mobile version 3.0.6 (3063),[26] Medscape database,[27] CURRENT Medical Diagnosis & Treatment 2024,[28] and pharmacotherapy textbooks (DiPiro[29] and Koda-Kimble[30]) were reference referred to evaluate drug selection and dosing appropriateness. Drug dosage and treatment regimens were assessed using the evidence-based UpToDate website.[31] We evaluated drug interactions with the Micromedex program[32]; only clinically significant interactions were classified as DTRPs. Treatment physicians were consulted, and pertinent laboratory investigations were used to raise the possibility of adverse drug reactions. The recorded DTRPs forms, including patients' profile forms, were periodically presented before the independent expert committee members to ensure the relevancy and appropriateness of DTRPs. An expert group consisting of an independent clinical pharmacist, a physician, and a nurse reviewed and evaluated the suspected DTRPs based on evidence sources. The DTRPs recorded on the drug-related problem documentation form verified by the expert committee were included for final analysis.

2.4. Data analysis

The recorded data for DTRPs were entered into Excel and SPSS V.29 software, and descriptive analyses were performed to analyze the data. The results were presented in frequency and percentage for categorical data and mean for continuous variables. Univariate and multivariate Binary logistic regression analysis was used to determine the influence of predictor variables on the occurrence of DTRPs. A confidence interval of 95% and p-value <0.05 was considered significant.

3. Results

During a three-month study period, 301 patients were enrolled, of which 161 (53.5%) were females. Most patients, 176 (58.5%), were in the age group of >64 years, belonging to the geriatric population. A total of 2818 medications were prescribed. The average number of drugs per patient was nine. During the hospital stay, 203 (67.4%) study participants received less than 11 drugs per patient. Patients' Demographic and clinical characteristics are presented in Table 1.

Of 301 study participants, 233 (77.4%) patients had DTRPs.

A total of 528 DTRPs were identified, with an average of 2.27±(0.92) DTRPs per patient in which, one DTRPs was identified in 54 (17.9%) patients, two DTRPs in 82 (27.2%), three DTRPs in 80 (26.6%) and more than three DTRPs in 17(5.7%) patients.

As per the PCNE problem categorization, treatment effectiveness accounts for 198 (37.5%), treatment safety 150 (28.41%), and other problems accounted for 180 (34.09%) of the total 528 problems identified in the study, as shown in Table 2.

Furthermore, 724 Causes have been identified among 233 patients who had DTRPs, with an average cause of 3.11±1.63. Drug selection

Table 1
Patient sociodemographic characteristics (n=301).

Characteristics	Category	Frequency (N=301)	Percentage (%)
Gender	Male	140	46.5
	Female	161	53.5
Age Group (Years)	13-19	10	3.3
(Mean age 60.29±17.9)	20-64	115	38.2
	≥65	176	58.5
Hospital Stays (Days)	2-4	69	22.9
(Mean Stay 6.8±3.4)	5-10	196	65.1
	>10	36	12.0
No. of Disease	1	104	34.5
(Mean 2.16±1.1)	2	96	31.9
	≥3	101	33.6
No. of drugs Prescribed	≤7	78	25.9
(Mean 9.4±3)	8-11	155	51.5
	>11	68	22.6

Table 2
Distribution of drug therapy related problems as per PCNE V9.1 Classification.

Code V9.1	Problem	No. of Problems	Percentage (%)
P1.1	No effect of drug treatment despite correct use	1	0.19
P1.2	Effect of drug treatment not optimal	166	31.4
P1.3	Untreated symptoms or indication	31	5.9
P1	**Treatment effectiveness**	**198**	**37.5**
P2.1	Adverse drug event (possibly) occurring	150	28.4
P2	**Treatment safety**	**150**	**28.41**
P3.1	Unnecessary drug-treatment	154	29.2
P3.2	Unclear problem/complaint	26	4.92
P3	**Other**	**180**	**34.09**
	TOTAL PROBLEMS	**528**	**100**

Table 3
Distribution of DTRPs cause as per PCNE V9.1.

Primary Domain	Code V9.1	Cause	Frequency	(%)
1. Drug selection	C1.1	Inappropriate drug according to guidelines/formulary	103	14.23
	C1.2	No indication for drug	94	12.98
	C1.3	Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	19	2.62
	C1.4	Inappropriate duplication of therapeutic group or active ingredient	21	2.90
	C1.5	No or incomplete drug treatment in spite of existing indication	41	5.66
	C1.6	Too many different drugs/active ingredients prescribed for indication	15	2.07
	C1	**Drug selection**	**293**	**40.47**
2. Drug form	C2.1	Inappropriate drug form/ formulation	14	1.93
	C2	**Drug form**	**14**	**1.93**
3. Dose selection	C3.1	Drug dose too low	18	2.49
	C3.2	Drug dose of a single active ingredient too high	27	3.73
	C3.3	Dosage regimen not frequent enough	17	2.35
	C3.4	Dosage regimen too frequent	33	4.56
	C3	**Dose selection**	**95**	**13.12**
4. Treatment duration	C4.1	Duration of treatment too short	62	8.56
	C4.2	Duration of treatment too long	59	8.15
	C4	**Treatment duration**	**121**	**16.71**
5. Dispensing	C5.1	Prescribed drug not available	3	0.41
	C5.2	Necessary information not provided or incorrect advice provided	111	15.33
	C5	**Dispensing**	**114**	**15.75**
6. Drug use process	C6.2	Drug under-administered by a health professional	22	3.04
	C6.3	Drug over-administered by a health professional	1	0.14
	C6.4	Drug not administered at all by a health professional	25	3.45
	C6.5	Wrong drug administered by a health professional	2	0.28
	C6	**Drug use process**	**50**	**6.91**
7. Patient related	C7.1	Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	18	2.49
	C7	**Patient related**	**18**	**2.49**
9. Other	C9.1	No or inappropriate outcome monitoring (incl. TDM)	18	2.49
	C9.3	No obvious cause	1	0.14
	C9	**Other**	**19**	**2.62**
		TOTAL	**724**	**100**

Table 4
Drug class involved in DTRPs.

S.N	Drug Class	Frequency	Percentage (%)
1	Antimicrobial Agent	362	55.18
2	Gastrointestinal Drugs	88	13.41
3	Respiratory System Drugs	55	8.38
4	Cardiovascular and Blood disorder Drugs	46	7.01
5	Antihistamines and NSAIDS	44	6.71
6	CNS Drugs	5	0.76
7	Others	56	8.54
	TOTAL	**656**	**100**

Note: "Other classes" include products such as Ayurvedic and nutraceuticals, which may have uncertain safety and efficacy, as well as other combination medications that do not fit clearly into a specific category.

problems accounted for 40.47% of the total reasons, followed by treatment duration (16.71%), dispensing (15.75%), and dose selection (13.12%), as shown in Table 3.

Similarly, A total of 95 drugs, 3 drug delivery devices, and 12 untreated indications were identified as the causes of DTRPs. Table 4 displays the classes of drugs that were involved in these DTRPs. Among them, antimicrobials accounted for the highest number of DTRPs, with 362 cases (55.18%), followed by gastrointestinal drugs with 88 cases (13.41%). Central Nervous System (CNS) drugs had the lowest number of DTRPs, with only 5 cases (0.76%).

The primary reasons contributing to DTRPs in our study included non-adherence to evidence-based medicine (EBM) and established guidelines. Key issues involved inappropriate drug selections and uses, such as antibiotics prescribed in contradiction to local and national antimicrobial treatment guidelines and the use of medications without valid indications. Additionally, Irrational drug use and therapeutic duplications were often noted during the study. Some examples of case-based problems are presented in Table 5.

Table 6 showed that the prevalence and risk of DTRPs were significantly greater in elderly patients, patients with comorbid conditions, patients who had longer hospital stay days, and patients taking polypharmacy ($p<0.05$). Furthermore, Multivariate binary logistic regression analysis showed that geriatric patients had a higher risk of experiencing DTRPs, with an adjusted odds ratio of 1.832 (1.021-3.286) at p-value < 0.05.

4. Discussion

In this study, Drug Therapy Related Problems (DTRPs) were identified in 77.4% (n=233) of patients. This percentage is comparable to the findings of similar studies conducted in the department of critical care medicine at a tertiary care hospital in Nepal (74.2%)[20] and in the medical ward of a referral hospital in northeast Ethiopia (75.51%).[33] Various factors may explain high prevalance of DTRPs in our study such as lack of monitoring, multiple physician prescribing, inadequate documentation in physicians/nursing cardex, and the lack of provision of Clinical Pharmacists as per the Hospital Pharmacy Guideline 2072[17] etc. The average number of DTRPs experienced per patient in this study was 2.27 ± (0.92). This is comparable to the DTRPs reported in a German university hospital (2.3)[34]and slightly higher than those found in medical wards of a referral hospital in northeast Ethiopia (1.08).[33] These findings highlight a high burden of DTRPs.

In this study, the majority of DTRPs were due to suboptimal drug treatment (31.4%), followed by unnecessary drug treatment (29.2%). This finding aligns with a prospective observational study conducted in a medical ward of a referral hospital in northeast Ethiopia, where the most common drug therapy problem was the need for additional drug therapy (35.85%) and unnecessary drug therapy (30.19%).[33] Further examination of the causes behind DTRPs showed that drug selection problems accounted for 40.47% of the total reasons, followed by treatment duration (16.71%), dispensing (15.75%), and dose selection (13.12%). This result is consistent with a study conducted in the Department of Critical Care Medicine of a tertiary care center in Nepal, where drug selection problems were the most common cause, accounting for 44.5% of the total reasons.[20] Unlike other studies, our study identified dispensing (15.75%) as one of the leading causes of problems due to the lack of counselling services, counselling spaces, qualified pharmacists, and clinical pharmacy services in the ward. Except for a few cases, almost all patients were unaware of how to use special medicine delivery devices like Meter Dose Inhalers, Rotahaler, and Insulin Pen or were using them incorrectly due to the absence of counselling services. This further emphasizes the crucial role of pharmacists in managing DTRPs.

The second highest percentage in the Drug Selection domain was the subcategory 'No Indication for Drug'. Antibiotics, antihistamines, and ursodeoxycholic acid were often prescribed without a valid indication, for symptomatic relief, or without clear evidence to support their use. This finding aligns with a study conducted in a hospital in Nepal, where antibiotics, cough suppressants, and gallstone-dissolving agents were identified as major contributors to DTRPs.[20] Similarly, the third highest percentage in the Drug selection domain is the subcategory of no drug treatment despite existing indications. This is due to the failure to receive medicine for preexisting chronic diseases such as Hypothyroidism, Diabetes mellitus, Hypertension, Chronic obstructive pulmonary disease, and other conditions like Anemia and Vitamin D insufficiency. The main reasons for this failure include the lack of efficient history taking, medication reconciliation, and patient's non-adherence towards their therapy. As a result, there is a high percentage of DTRPs at discharge and admission. This finding is consistent with previous studies that have shown that the omission of drugs is a common medication error on discharge prescriptions from the hospital.[35,36] Another study also found that around 16.7% of patients were not receiving drug treatment despite having an existing indication at admission.[5] Therefore, pharmaceutical care services such as medication reconciliation are very useful during hospital admission and discharge.[35,37]

Patient-related causes accounted for only 2.49% of the total cause. This is because post-discharge adherence was not measured, and the responsibility for administering drugs during the patient's stay in the ward fell on the nurses. The majority of patient-related causes were attributed to the unavailability of medication for administration by the patient's caregiver. This was primarily due to the patients' poor financial condition, the caregiver's inability to procure medication, the patient's forgetfulness, and the patient's perception and attitude towards medication. These findings contrast with previous studies, such as the study conducted by Gashaw Binega Meknonnen et al., where non-compliance was found to be the second most common drug-related problem, accounting for 28.9% of cases.[38] Another study conducted at Adama Hospital Medical College in East Ethiopia also revealed different findings, indicating that non-adherence was the second most prevalent DTRPs, surpassed only by drug interaction.[39]

In this study, 2.62% of the total DTRPs are attributed to other causes. Contributing to this were some instances of insufficient monitoring of outcomes, particularly for narrow therapeutic drugs such as Warfarin, lithium carbonate, digoxin, and vancomycin. The absence or insufficiency of Therapeutic Drug Monitoring (TDM) services can be largely attributed to the lack of qualified personnel, facilities, and well-equipped laboratories for TDM. This finding is consistent with previous studies highlighting the absence of TDM services in Nepal[18] and their limited progress in many other developing countries.[40]

Furthermore, the study findings reveal that the majority of DTRPs are caused by drug selection (40.47%) followed by treatment duration (16.71%), dispensing (15.75%), and dose selection (13.12%). This finding is comparable to other studies where drug selection is the most frequent cause.[4,20] This suggests that a significant number of DTRPs can be prevented by proper drug selection and rational drug use, following evidence-based knowledge, local and national antimicrobial guidelines, and various guidelines such as Beer's criteria. Other

Table 5
Case-based Examples of the DTRPs.

Primary domain (PCNE Code)	Cause (PCNE Code)	Examples of patients identified with specified DTRP	Comments/Recommendation
Drug selection (C1)	Inappropriate drug according to guidelines/ formulary (C1.1)	*Case 1:* A 17-year-old male with known Type 1 Diabetes Mellitus (T1DM), diagnosed with Diabetic Ketoacidosis (DKA) was prescribed Metformin 500 mg orally twice daily.	Metformin is contraindicated for diabetic ketoacidosis with or without coma.
		Case 2: A 90-year-old female was admitted for an acute exacerbation of chronic obstructive pulmonary disease (AE of COPD), presenting with shortness of breath, cough, and delirium. She was prescribed Ranitidine 150 mg orally twice daily for stress ulcer prophylaxis.	Beers Criteria recommends avoiding the use of Ranitidine in patients with or at high risk of delirium as histamine H2 receptor antagonists may induce or worsen delirium.
	No indication of drug (C1.2)	*Case 1:* A 52-year-old male was admitted with shortness of breath (SOB) and cough and was diagnosed with congestive cardiac failure (CCF). However, prescription with Levocetirizine and Montelukast was found to be taken orally at bedtime.	Levocetirizine and Montelukast offer no benefit for SOB and cough caused by CCF.
	Inappropriate combination of drugs (C1.3)	*Case 1:* A 66-year-old male with a known history of hypertension was diagnosed with a stroke. He was prescribed Clopidogrel 75 mg and Esomeprazole 40 mg simultaneously.	Esomeprazole can decrease the serum concentrations of Clopidogrel's active metabolite(s) (Major interaction)
	Inappropriate duplication of the therapeutic group or active ingredient (C1.4)	*Case 1:* A 46-year-old female was admitted to the ward with Chicken Pox. The physician prescribed either Acyclovir or Valacyclovir, but due to illegibility in prescription, the nurse incorrectly transcribed both medications onto the nurse cardex. As a result, the patient received both drugs, leading to duplication.	Acyclovir and Valacyclovir are both effective treatments for Chicken Pox. However, taking both drugs simultaneously results in duplication.
	No or incomplete drug treatment despite existing indication (C1.5)	*Case 1:* A 56-year-old male with a known case of hypothyroidism (taking Thyroxine 25mcg) was diagnosed with acute exacerbation of chronic obstructive pulmonary disease. Unfortunately, no thorough medical history was taken during admission. Consequently, the patient did not receive Thyroxine despite its indication.	Comprehensive medical and medication history was not obtained, resulting in incomplete treatment of co-morbidity.
Drug form (C2)	Inappropriate drug form /formulation (for this patient) (C2.1)	*Case 1:* A 17-year-old female was admitted with complaints of shortness of breath and was diagnosed with rheumatic heart disease (RHD) with severe mitral regurgitation (MR). Her prescription contains oral Phenoxymethyl penicillin, whereas intramuscular Benzathine Penicillin 1.2M is the preferred choice of drug.	Intramuscular Benzathine Penicillin 1.2M is preferred due to its sustained release, offers convenience and improves treatment adherence.
Dose selection (C3)	Drug dose too low (C3.1)	*Case 1:* A 62-year-old male was admitted with chronic kidney disease (CKD) and a phosphate concentration of 8.6 mg/dL. The doctor prescribed Sevelamer 800mg orally twice daily.	If the serum phosphorus level is between 7.5 to <9 mg/dL, the recommended Sevelamer dose is 1200 to 1600 mg three times daily with meals.
		Case 2: A 77-year-old female was admitted with congestive cardiac failure (CCF). Empagliflozin at a dose of 5mg orally once daily was prescribed, along with other evidence-based medical therapies.	Evidence-based medicine (EBM) recommends taking Empagliflozin at a dose of 10 mg orally once daily in the morning for heart failure.
	Drug dose of a single active ingredient too high (C3.2)	*Case 1:* A 72-year-old male with a known history of Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) was diagnosed with Community-acquired pneumonia (CAP). The patient's creatinine clearance (CrCL) is 35 ml/min. The doctor prescribed 500 mg of Levofloxacin intravenously once daily for CAP. Given his renal function, this dose is too high for this patient.	Evidence-based medicine (EBM) recommends Levofloxacin 500 mg intravenously or orally every 24 hours for 7 to 14 days for CAP. For patients with a CrCL of 20 to 49 mL/min, the recommended dosage is 500 mg initially, followed by 250 mg every 24 hours.
	Dosage regimen not frequent enough (C3.3)	*Case 1:* A 65-year-old female was diagnosed with acute pyelonephritis and renal impairment (CrCL 41 mL/min). She was prescribed Imipenem (500 mg) + Cilastatin (500 mg) intravenously twice daily. However, this frequency is insufficient for her medical condition.	Evidence-based medicine (EBM) recommends Imipenem (500 mg) + Cilastatin (500 mg) every 6 hours for pyelonephritis. If creatinine clearance (CrCL) is between 30 and 60 mL/min, the dosage should be adjusted to 500 mg every 8 hours.
	Dosage regimen too frequent (C3.4)	*Case 1:* A 70-year-old male with an acute exacerbation of chronic obstructive pulmonary disease (AE of COPD) and renal impairment (CrCL 12 mL/min). Cefuroxime 500 mg orally twice daily for 7 days was found administered. Given his renal status, this frequency is too frequent.	Evidence-based medicine (EBM) recommends that if creatinine clearance (CrCL) is between 10 and 30 mL/min, the dose of Cefuroxime for AE of COPD should be 500 mg once daily.
Treatment duration (C4)	Duration of treatment too short (C4.1)	*Case 1:* A 57-year-old male was tested positive for H. pylori. During his hospital stay, the physician initiated a triple drug therapy regimen for H. pylori eradication. The patient was discharged after 6 days, but the anti-H. pylori regimen was omitted from his discharge medications.	Evidence-based medicine (EBM) recommends an anti-H. pylori regimen for 10 to 14 days to achieve eradication.
	Duration of treatment too long (C4.2)	*Case 1:* A 76-year-old male was diagnosed with an acute exacerbation of chronic obstructive pulmonary disease (AE of COPD). The physician prescribed Azithromycin 500 mg once daily, and the patient received it for 3 days. Upon discharge, another doctor prescribed it for an additional 3 days, resulting in a total duration of 6 days, which is longer than recommended.	Evidence-based medicine (EBM) recommends Azithromycin 500 mg orally once daily for 3 days to treat AE of COPD.

(*continued on next page*)

Table 5 (*continued*)

Primary domain (PCNE Code)	Cause (PCNE Code)	Examples of patients identified with specified DTRP	Comments/Recommendation
Dispensing (C5)	Prescribed drug not available (C5.1)	*Case 1:* A 55 years chronic alcoholic male was admitted with Chronic liver disease (CLD) and developed alcohol withdrawal syndrome (AWS) at medical ward and Doctor prescribed Inj. Lorazepam IV 2mg for AWS. But this medicine was not available locally.	Lack of many registered product (only LOPEZ-INJECTION2 MG IP is registered) and strict regulatory requirements for Narcotics and Psychotropics make them unavailable.
	Necessary information not provided or incorrect advice provided (C5.2)	*Case 1:* Patients were not counselled or poorly counselled about Special medicine delivery devices like metered dose inhaler (MDI), Rota haler, Insulin pen because of lack of counselling facilities and trained staffs and patients were found to be incorrectly using such device.	Incorrect use of such devices leads to therapeutic failure from under administration or Adverse Drug Reactions (ADR) from over administration.
Drug use process (C6)	Drugs are not administered at all by a health professional (C6.4)	*Case 1:* A 30-year-old female was admitted with severe urinary tract infection (UTI), and the doctor prescribed Amikacin (750 mg) intravenously once daily. However, on some days, the nurse did not administer the medication due to workload constraints.	A busy workload, delegation of tasks to students, and improper documentation were identified as the leading causes of errors in the drug use process.
Patient related (C7)	Patient does not take the drug at all for whatever reason (C7.1)	*Case 1:* A 53-year-old male was admitted with liver failure associated Hypoalbuminemia (2.3g/dl), Doctor prescribed Albumin (20%).	Poor economic condition of patient and expensive nature of drug patient caregiver was not able to make drug available.
Other (C9)	No or inappropriate outcome monitoring (incl. TDM) (C9.1)	*Case 1:* Various Narrow Therapeutic Index Drugs (Warfarin, Lithium carbonate, Digoxin, Vancomycin etc) which requires Therapeutic drug monitoring (TDM) were not found to be done TDM.	Lack of TDM facilities.

measures include conducting drug therapy reviews by clinical pharmacists, ensuring proper documentation of patient case sheets, physician and nursing cardex, dose adjustment in special populations like renal failure, and providing well-facilitating counselling services to patients.

In our study, antimicrobials (55.18%), such as Azithromycin, Levofloxacin, Piperacillin + Tazobactam, and Ceftriaxone, are the major culprits for DTRPs. Many antimicrobials were not found to have been prescribed in adherence to national and local antimicrobial treatment guidelines, which may predispose patients to the risk of antimicrobial resistance. Therefore, following and implementing antimicrobial prescribing guidelines is crucial to ensure rational antimicrobial therapy. Our findings align with several other studies where antibiotics accounted for a high percentage of DTRPs, ranging from 75% in the University of Gondar Teaching Hospital in Northwest Ethiopia,[38] 59.1% in the medicine ward of a tertiary care hospital in Eastern Nepal,[23] to 55% in the department of critical care medicine of a tertiary care centre in Nepal.[20] Previous studies have also reported the irrational use of antibiotics in Nepal,[15,16] and the present study reinforces antibiotics as the primary group of medicines contributing to DTRPs. Multiple studies have examined antibiotic use in hospitals and the prevalence of antimicrobial resistance is high.[41,16] One possible reason for antibiotics contributing to a higher number of DTRPs is the empirical prescribing of multiple antibiotics without culture and sensitivity testing, as well as the failure to adhere to local, national, and international antimicrobial prescribing guidelines. Additionally, the lack of an arrangement for maintaining antibiograms for hospitals, coupled with poor data management and retrieval, may contribute to this issue.

Similarly, our study found a statistically significant relationship between the presence of DTRPs and the number of diseases, length of hospital stay, number of prescribed drugs, and elderly, which is in line with the findings of most previous studies.[42,38,43] However, the results of the binary logistic regression indicate a significant prevalence of DTRPs among geriatric patients. These findings may be attributed to age-related changes in pharmacokinetics and pharmacodynamics, multiple comorbidities, and polypharmacy in geriatric patients.[44] Several studies have also concluded that geriatric patients who take multiple medications are more prone to developing DTRPs.[45,46]

4.1. Strengths and limitations

One of the study's strengths is that it used PNCE recommendations to assess Drug Therapy Related Problems in medical wards of tertiary care hospitals in eastern Nepal for the first time, shedding insight into the frequency and root causes of DTRPs. Furthermore, to ensure that all DTRPs and their causes were thoroughly identified for their clinical relevance, this study also used independent expert committee verification to assess and evaluate the identified DTRPs. However, the study has certain limitations in that it was conducted solely in a single-centre medicine ward, which could limit its generalizability. Additionally, the study did not assess post-discharge adherence or consider other

Table 6
Results of univariate and multivariate binary logistic regression analysis between selected predictor variables with DTRPs.

Variables	Category	DTRPs		COR (95% CI)	P-value	AOR (95% CI)	P-value
		Yes (n=233)	No (n=68)				
Gender	Male	105 (45.1%)	35 (51.5%)	0.773 (0.450-1.329)	0.352	-	-
	Female	128 (54.9%)	33 (48.5%)	1			
Geriatric	Yes	123 (52.8%)	24 (35.3%)	2.05 (1.171-3.589)	0.012*	1.831 (1.022-3.280)	0.042*
	No	110 (47.2%)	44 (64.7%)	1		1	
No. of Disease	>2	87 (37.3%)	14 (20.6%)	2.298 (1.206-4.381)	0.011*	1.613 (0.794-3.276)	0.186
	≤2	146 (62.7%)	54 (79.4%)	1		1	
Hospital Stay	≥7	107 (45.9%)	20 (29.4%)	2.038 (1.139-3.647)	0.016*	1.714 (0.919-3.199	0.090
	<7	126 (54.1%)	48 (70.6%)	1		1	
No of Drug	>7	179 (76.8%)	44 (64.7%)	1.808 (1.009-3.239)	0.046*	1.227 (0.653-2.306)	0.525
	≤7	54 (23.2%)	24 (35.3%)	1			

AOR: Adjusted odds ratio; COR: Crude odds ratio; CI: Confidence Interval.
* Shows significant at p-value <0.05.

domains, such as planned interventions, acceptance of the intervention, and the DTRPs status of PCNE V9.1. Furthermore, the three-month duration might not adequately capture seasonal variations.

5. Conclusion

This study highlights the significant prevalence of Drug Therapy Related Problems (DTRPs) in the general medicine ward of a tertiary care hospital in Eastern Nepal, with nearly three-fourths of hospitalized patients experiencing at least one DTRPs. The most frequent causes of DTRPs were related to drug selection, treatment duration, and inappropriate dosing, with antimicrobials being the most common drugs involved. Advancing age, polypharmacy, comorbidities, and prolonged hospital stays are significant predictors of DTRPs. Clinical pharmacists play an important role in early detection, prevention, and resolution of DTRPs, and their involvement in healthcare teams could positively influence clinical outcomes. Many DTRPs are preventable; therefore, establishing comprehensive pharmaceutical care services and enhancing awareness training related to rational drug use to health professional training in hospitals is recommended.

5.1. Recommendation for policy, practice, and educators

- Clinical pharmacists play a crucial role in inpatient care by enhancing patient drug therapy outcomes and safety through early detection and prevention of medication issues. Hospitals should enforce strict regulations and policy reforms to mandate the integration of clinical pharmacy services in the medical wards.
- Given the high prevalence of preventable DTRPs, clinical pharmacists should focus on and prioritize patients with advancing age, comorbidities, polypharmacy, or extended hospital stays for drug therapy review to optimize medication safety among those patients.
- Pharmacy education programs should integrate comprehensive curricula and practice-based modules particularly focused on subjects related to pharmacotherapeutics and incorporate the provision of extended clinical pharmacy internship programs in the hospital to develop competencies and skills required for clinical pharmacy practices for ensuring safe, effective, and rational drug therapy in hospital clinical settings.

CRediT authorship contribution statement

Rahi Bikram Thapa: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Prasanna Dahal:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Subash Karki:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Uttar Kumar Mainali:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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