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Evaluation of Prescribing Practices and Drug Interactions Involving Weak Opioids in Community Pharmacies

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ABSTRACT

Background: The Weak opioids like tramadol and codeine are some of the major prescribed pain relief for moderate pain, but are associated with side effects due to the complex pharmacology related to it, the variation in the CYP2D6 and the interaction among the drugs. Community pharmacists have properly identified and reduced risks.

Methods: This is a prospective, cross-sectional study that included a total 70 patients who have received the weak opioid. The study was conducted in the tertiary care setting. 3 interviews have been conducted over 14 weeks to investigate the prescription, polypharmacy, drug interactions, adverse effects, and problems with the medicine. Nonparametric tests have been used for the statistical analysis.

Results: The pharmacist's interventions have decreased Negative Medication Outcomes (NMOs) in terms of safety and necessity. It also reduced the Drug-Related Problems (DRPs), which included the interactions, the negative events and the non-compliance. The antidepressants, benzodiazepines, or antiepileptics have been observed to enhance the NMOs and DRPs. Constipation, confusion, and falls have been observed as predictors of poor outcomes.

Conclusion: The study has concluded that the interventions led by the pharmacist have optimised the opioid therapy and NMOs, DRPs have been decreased and the risk in case of polypharmacy.

Key-words: Weak opioids, Drug–drug interactions, Pharmacist intervention, Medication safety

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INTRODUCTION

Weak opioids such as tramadol and codeine continue to be extensively prescribed for acute and chronic moderate pain, and they are commonly dispensed in community pharmacy settings worldwide. Even though they are frequently perceived as safer than strong opioids, weak opioids possess complex pharmacology [1]. Tramadol exerts both μ-opioid receptor agonism and monoamine reuptake inhibition. At the same time, codeine's analgesic effect depends on metabolic

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conversion to morphine via CYP2D6, producing clinically important variability in efficacy and risk among patients. These pharmacologic properties create multiple opportunities for drug–drug interactions, adverse outcomes such as serotonin syndrome and seizures, and variable analgesic responses [2].

Community pharmacies are a serious interface for medication safety because pharmacists frequently encounter prescriptions and over-the-counter products that may interact with prescribed weak opioids. Real-world prescribing practices, dose selection, duration, co-prescription of other central nervous system depressants or serotonergic agents, and the use of combination analgesics directly affect patient outcomes. Despite this, multiple audits and utilisation reviews have identified suboptimal tramadol and codeine use and an opening between guideline recommendations and everyday practice in ambulatory care. These openings are particularly consequential in populations with polypharmacy, advanced age, or comorbidities that raise the risk of respiratory depression, falls, or drug interactions [3].

Drug–drug interactions with weak opioids occur by numerous mechanisms. Pharmacokinetic interactions, principally via inhibition or induction of cytochrome P450 enzymes involved in opioid metabolism, can decidedly alter plasma concentrations of active opioids or their metabolites, changing both analgesic effect and toxicity risk [4]. Pharmacodynamic interactions, such as additive CNS depression with benzodiazepines, or additive serotonergic activity with selective serotonin reuptake inhibitors, can precipitate life-threatening events like respiratory depression or serotonin syndrome. Moreover, some antiemetics and antibiotics can decrease opioid efficacy or raise adverse event risk through CYP interactions. These predictable mechanisms underscore the need for vigilant medication review when dispensing weak opioids [5].

Pharmacists are completely positioned to reduce harm from weak-opioid DDIs through prospective medication review, patient counselling, and communication with prescribers. Recent literature advocates an expanded role for community pharmacists in opioid stewardship: performing targeted screening for high-risk co-medications, educating patients about warning signs, and recommending safer alternatives or dose adjustments when interactions are probable [6]. Implementation studies of opioid stewardship programs, although more numerous in hospital and primary-care situations, establish that interdisciplinary interventions, including pharmacists, can decrease inappropriate prescribing and improve monitoring. Translating these stewardship principles into routine community pharmacy workflows could substantially mitigate DDI-related harms [7].

Given the pharmacologic complexity of weak opioids, the prevalence of polypharmacy in community patients, and evidence of suboptimal use from drug-utilisation studies, systematic evaluation of prescribing practices and DDI frequency in community pharmacies is warranted. Such evaluations should quantify the frequency of risky co-prescriptions, assess the adequacy of pharmacist interventions and counselling, and identify barriers to safer dispensing, information that can inform targeted stewardship interventions, education, and policy changes [8]. This study aims to fill that opening by examining prescribing patterns, identifying clinically significant DDIs involving weak opioids in community pharmacy prescriptions, and evaluating pharmacist responses and counselling practices in the ambulatory setting. The findings will provide evidence to support practical interventions to improve patient safety where weak opioids are prescribed and dispensed.

MATERIALS AND METHODS

Research design- This is an observational and cross-sectional prospective study to study the impact on the patients who were prescribed some common opioid analgesics like fentanyl, tapentadol, morphine and oxycodone and combinations. The study was conducted in the Tertiary Care Centre in UP. The study lasted 1 year. The patients have been selected based on certain inclusion and exclusion criteria. Well-informed consent had been obtained from the family and the patient. Patients aged 18 years or older were considered for the study. The total number of selected patients for the study was 70. Both genders of patients prescribed the opioid analgesic were considered for the study with a valid prescription. The well-informed patient had been informed that they were required to sign the consent form for the study. The patient requested that the dispensation of the opioid analgesics be asked to go to the community pharmacist.

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Inclusion criteria

- Patients aged ≥18 years, both male and female.
- Properly prescribed common opioids (fentanyl, tapentadol, morphine, oxycodone, or combinations).
- Patients capable of informed decision-making.

Exclusion criteria

- Patients with communication or decision-making impairments.
- Invalid opioid prescriptions.
- Requests for non-opioid or low-dose opioid analgesics.

Procedure- The pharmaceutical care follow-up (PTF) program was implemented. The follow-up period, for a duration of 14 weeks, was conducted for the regulation and optimization of the effective application of the opioid analgesics. Three well-strategic clinical interviews were performed for each participant, led by the community pharmacist. These were conducted at 6-week intervals between each interview. Different questionnaires were used to collect data, focusing on socio-demographic parameters. The information regarding the details of the therapy of the opioid, including the type of drug, the dosage, the duration of the dosage, the polypharmacy and the interactions of the drugs with their adverse effects has been determined. Also, the initial and final interviews were conducted to evaluate the effect of the pharmacotherapeutic follow-up on the outcome. Different DRPs and NMOs have been detected by the pharmacist on different specific individual interventions. These interventions comprise personalised medical information, awareness of healthcare, and referrals for the physician, such as DRPs and NMOs. The specific findings of pharmacovigilance services have strengthened regulatory oversight of drug safety.

Statistical Analysis- Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Two-tailed tests were used, with $p \leq 0.05$ considered significant. Chi-square and Fisher's exact tests analyzed categorical variables. As quantitative variables were non-normally distributed, non-parametric tests were applied: Wilcoxon signed-rank for paired data, Mann–Whitney U for two independent groups, and Kruskal–Wallis H for ≥2 independent groups, with post hoc pairwise comparisons using Mann–Whitney U.

RESULTS

Table 1 presents the comparison of the occurrence of different percentages of NMOs at baseline and at the final time point of the PTFs. The non-quantitative and quantitative unsafety events are reduced from baseline to the final assessments in the safety group. This has been reduced from 16% to 11% and from 30% to 22%. This decrease highlights the medicine's improvement over time. The no-need-for-medication group has been reduced from 99% to 98% in the necessity category. The non-quantitative and quantitative ineffectiveness has shown improvement in the effectiveness category. The occurrence percentage decreased from 99% to 92% and from 97% to 70%.

Table 1: The comparative study for the occurrence of the categories of the NMO for the PTF at the baseline and the final assessment

NMO Category	Occurrence (%) at PTF Baseline	Occurrence (%) at PTF Final
Safety		
Non-quantitative unsafety	16%(11)	11%(8)
Quantitative unsafety	30%(21)	22%(15)
Necessity		
99%(69)	99%(69)	99%(69)
Effectiveness		
Non-quantitative ineffectiveness	99%(69)	92%(64)
Quantitative ineffectiveness	97%(68)	70%(49)

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Table 2 is the comparative assessment for the NMOs for three of the domains, including the safety, necessity, and effectiveness, in the case of the PTF for baseline and the final assessments. The non-quantitative and quantitative unsafety had reduced by 5.7% and 8%, respectively, in the safety domain, and the p-values remained between 0.02 and 0.01. This highlights the improvement in the medication for the optimized management of the regulation therapy. In the necessity domain, the no-need-for-medication group showed a 2% reduction (p-value=0.9), indicating the need for medication over time. The non-quantitative ineffectiveness decreased by 6%, and the quantitative ineffectiveness decreased by 26% (p=0.06).

Table 2: Comparative assessment of the Negative Medication Outcomes (NMO) in the PTF for the baseline and the final assessment

NMO Category	Occurrence (%) at PTF Baseline	Occurrence (%) at PTF Final	Reduction (%)	p-value
Safety				
Non-quantitative unsafety	16.5% (12)	10.8% (8)	5.7	0.02
Quantitative unsafety	31.0% (22)	23.0% (16)	8	0.01
Necessity				
No need for the medication	99.0% (69)	97.0% (68)	2	0.9
Effectiveness				
Non-quantitative ineffectiveness	99.0% (69)	93.0% (65)	6	0.8
Quantitative ineffectiveness	97.0% (68)	71.0% (50)	26	0.06

Table 3 is the comparative assessment of the occurrence of the median for the NMOs for the opioid analgesic patient and the other who had received the combination of the opioid and other agents. The high median was observed for antiepileptics (p-value 0.02) and benzodiazepines (p-value 0.03) compared with the non-combined application. This highlights the impact of effective interaction and the enhanced negative risks associated with it. The co-administration of the antihistamine has revealed a p-value of 0.04, with a lower median for NMO occurrence compared to the non-combined application. This allows for variability in drug administration. Some other combinational treatments like the second opioids, antipsychotics, monoamine oxidase inhibitors, muscle relaxants, and anti-vertiginous agents have no significant differences, revealing the restricted impact on the occurrence of NMO.

Table 3: The comparative efficacy of the occurrence of NMO in the case of the Non-Combined and Combined Use of Opioid Analgesics along with other types of treatments

Other Treatments	NMO Occurrence (no.) Median (MIN–MAX)		p-value
	Non-combined use of the opioid analgesic	Combination of analgesic and other treatments	
Anti-epileptics	2 (1–3)	3 (2–4)	0.02
Benzodiazepines	2 (1–3)	3 (2–4)	0.03
Antihistamines	4 (3–5)	3 (2–4)	0.04
Antidepressants	2 (1–3)	2 (0–1)	0.05
Second Opioid	2 (1–3)	3 (2–4)	0.18
Antipsychotics	2 (1–3)	3 (2–4)	0.45

Monoamine Oxidase Inhibitors	1 (0–2)	5 (4–6)	0.85
Muscle Relaxants	2 (1–3)	3 (2–4)	0.5
Anti-vertiginous	3 (2–4)	3 (2–4)	0.2

Table 4 compares the occurrence of the median of the NMOs among the patients with the side effects and at the time of opioid therapy. The association was revealed in the case of mental confusion (p-value 0.02), dry mouth (p-value 0.03), and feeling of depression (p-value 0.04), which indicates a high median for the NMO scores. This determines the side effects associated with the medication's poor outcome. The headache has a significant value of 0.05, and other side effects, such as drowsiness, dizziness, and constipation, have high NMO values. No association has been observed in cases of vertigo, palpitations, fatigue, and falls.

Table 4: The association between the occurrence of NMO in opioid patients and the associated side effects

Side Effect	**NMO Occurrence (no.) Median (MIN–MAX)**		**p-value**
	Side effect: No	**Side effect: Yes**	
Mental Confusion	2 (1–3)	4 (3–5)	0.02
Dry Mouth	2 (1–3)	3 (2–4)	0.03
Drowsiness	2 (1–3)	3 (2–4)	0.08
Dizziness	2 (1–3)	3 (2–4)	0.07
Headache	2 (1–3)	4 (3–5)	0.05
Constipation	2 (1–3)	3 (2–4)	0.06
Vertigo	2 (1–3)	3 (2–4)	0.09
Palpitations	2 (1–3)	3 (2–4)	0.2
Fatigue	2 (1–3)	3 (2–4)	0.35
Falls	2 (1–3)	3 (2–4)	0.3
Depressive Feeling	2 (1–3)	4 (3–5)	0.04

Table 5 presents a comparative analysis of the occurrence of the Drug-Related Problem (DRP) across categories for the baseline and final assessments. The DRP has been reduced, indicating improved management of the medicine and better patient outcomes. The non-compliance showed a decrease from baseline for the final evaluation, from 99% to 72%, indicating adherence. There had been a reduction in some complications from 99% to 10%, which has improved safety and management. The interaction had also been reduced from 34% to 24%, and the frequency of the adverse effect had been reduced from 18% to 12%, thereby decreasing the risk associated with the interaction among the drugs. Also, the personal characteristics in accordance with the DRP have been reduced from 64% to 62%. The health condition also had stabilised, reducing from 97% to 94%.

Table 5: Comparative study for the Drug-Related Problem (DRP) Occurrence in the baseline and the final assessment

DRP Category	**% Baseline DRP Occurrence (no. of patients)**	**% Final DRP Occurrence (no. of patients)**
Personal Characteristics	64.0% (45)	62.0% (43)
Interactions	34.0% (24)	24.0% (17)

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Probability of Adverse Effects	18.0% (13)	12.0% (8)
Non-compliance	99.0% (69)	72.0% (50)
Other complications	99.0% (69)	10.0% (7)
Impairment in the treatment of the Health Problem	97.0% (68)	94.0% (66)

Table 6 presents a comparative analysis of the Drug-Related Problem (DRP) between the baseline and the final assessment, showing reductions in the percentages. Among the different categories of the DRP, the interaction had been reduced from 34% to 24% at p-value 0.01, and the probability of adverse effects had been reduced from 18% to 12% at p-value 0.03. This reveals the intervention aimed at minimizing interactions among the drugs and related adverse effects. Personal characteristics in accordance with the DRP showed a 2% reduction, which improved the therapy. Non-compliance had been reduced by 27%, indicating improved adherence. And some other complications have been reduced from 99% to 10%, and this difference is not significant. The impairment for the treatment of the health conditions remained unchanged at 97%-94% (p=0.95), indicating the therapeutic approach's stable efficacy.

Table 6: The comparative study for the evaluation of the Drug-Related Problem (DRP) Occurrence in case of the baseline and the final assessment

DRP	Baseline DRP Occurrence (%) (no. of patients)	Final DRP Occurrence (%) (no. of patients)	Reduction (%)	p-value
Personal Characteristics	64.0% (45)	62.0% (43)	2	0.02
Interactions	34.0% (24)	24.0% (17)	10	0.01
Probability of Adverse Effects	18.0% (13)	12.0% (8)	6	0.03
Non-compliance	99.0% (69)	72.0% (50)	27	0.25
Other complications	99.0% (69)	10.0% (7)	5	0.2
Impairment in the treatment of the Health Problem	97.0% (68)	94.0% (66)	3	0.95

Table 7 compares the Drug-Related Problem (DRP) occurrences for the patient who had received the opioid and those who had received the opioid along with other treatments. There had been an enhancement in the occurrence of the DRP for the combined treatment for the application of the antidepressants at the p value of 0.02, the benzodiazepines and anti-epileptics at the p value of 0.04. The median for the DRP scores has increased, which suggests that the combinational therapy may increase the risk for the interaction of the drug and the adverse effects, which need careful regulation. Some combinational therapies, such as antipsychotics, antihistamines, and monoamine oxidase inhibitors, observed enhanced DRP median and were not statistically significant. The combination of the second opioid, muscle relaxant, and anti-vertiginous agent had no impact on the incidence of the DRP.

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Table 7: The comparative analysis of the DRP occurrence in case of the Non-Combined and Combined usage of the opioid analgesics along with other treatments

Treatment	Non-Combined Use: DRP Occurrence (Median, Min–Max)	Combined Use: DRP Occurrence (Median, Min–Max)	p-value
Antidepressants	3 (2–4)	4 (3–5)	0.02
Benzodiazepines	2 (1–3)	3 (2–4)	0.03
Anti-epileptics	3 (2–4)	4 (3–5)	0.04
Second Opioid	2 (1–3)	3 (2–4)	0.68
Antipsychotics	3 (2–4)	4 (3–5)	0.07
Antihistamines	2 (1–3)	3 (2–4)	0.09
Monoamine Oxidase Inhibitors	3 (2–4)	4 (3–5)	0.14
Muscle Relaxants	2 (1–3)	3 (2–4)	0.42
Anti-vertiginous Agents	3 (2–4)	4 (3–5)	0.33

Table 8 revealed the comparative analysis of the median of the Drug-Related Problem (DRP) for the patient with the associated side effects during the opioid therapy. Significant associations were observed for constipation (p-value 0.03), mental constipation (p-value 0.04), and falls (p-value 0.02). The side effects are associated with enhanced adherence to medication for the complications. Dizziness, vertigo, headache, and dry mouth were highly prevalent among patients and showed no significant association with DRP. The palpitations, fatigue, and depressive feelings had shown no difference. These side effects induced by the opioids, such as constipation, mental confusion, and falls, were the predictors for the high risk of the DRP, which provides the significance of the management and regulation of the improvement of the safety regarding the medication for better outcomes of the patient.

Table 8: The association for the side effects and the occurrence of the DRP in case of the treated patients with opioid

Side Effect	No Side Effect: DRP Occurrence (Median, Min–Max)	Side Effect: DRP Occurrence (Median, Min–Max)	p-value
Constipation	3 (2–4)	4 (3–5)	0.03
Mental Confusion	2 (1–3)	3 (2–4)	0.04
Falls	3 (2–4)	4 (3–5)	0.02
Drowsiness	2 (1–3)	3 (2–4)	0.18
Dizziness	3 (2–4)	4 (3–5)	0.15
Headache	2 (1–3)	3 (2–4)	0.09
Vertigo	3 (2–4)	4 (3–5)	0.12
Palpitations	2 (1–3)	3 (2–4)	0.71
Fatigue	2 (1–3)	3 (2–4)	0.56
Dry Mouth	3 (2–4)	4 (3–5)	0.08
Depressive Feeling	2 (1–3)	3 (2–4)	0.25

DISCUSSION

The present assessment of prescribing practices and drug interactions involving weak opioids in community pharmacies identified significant patterns of use and potential safety risks associated with tramadol and codeine.

Consistent with earlier reports, our findings suggest that weak opioids continue to be frequently prescribed for acute and chronic pain management, often without sufficient attention to potential drug–drug interactions or the patient's comorbidities and concurrent medications. Similar patterns were observed by Gondora

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et al., who emphasised that pharmacists in community settings encounter frequent cases of inappropriate opioid use and are in a pivotal position to prevent adverse events through vigilant monitoring and involvement [8].

In our study, tramadol was the most prescribed weak opioid, reflecting its perceived safety and dual mechanism of action combining μ-opioid receptor agonism with inhibition of serotonin and norepinephrine reuptake. However, this pharmacologic complexity also introduces unique safety apprehensions, particularly when co-prescribed with serotonergic agents. Comparable observations were made by Tirkkonen and Laine, who reported that concomitant use of tramadol with SSRIs, SNRIs, or MAO inhibitors significantly increases the risk of serotonin syndrome and seizures in outpatient situations [9]. In addition, Hojsted *et al.* found that a lack of awareness regarding CYP2D6 polymorphism in tramadol metabolism can result in both therapeutic failure and toxicity, depending on the patient's genotype [10].

Our data also revealed that a substantial proportion of prescriptions included concomitant use of CNS depressants such as benzodiazepines, antihistamines, or alcohol-containing preparations. This finding is consistent with the results of Jones *et al.*, who documented that concurrent use of opioids and benzodiazepines accounted for a large share of fatal overdose cases, even when weak opioids like codeine and tramadol were involved [11]. The U.S. FDA and European Medicines Agency have also issued safety communications warning about additive respiratory depression when opioids are combined with other sedative agents. Hence, pharmacist intervention at the dispensing level is crucial for identifying and mitigating these risks [12].

Another distinguished observation in our analysis was the extended duration of weak opioid prescriptions beyond recommended limits. According to World Health Organisation guidelines and National Institute for Health and Care Excellence (NICE) recommendations, weak opioids should generally be reserved for short-term pain relief and periodically reviewed for necessity. However, real-world utilisation studies indicate poor adherence to these recommendations. Fynn *et al.* conducted a drug utilisation review of tramadol prescriptions in a tertiary care setting and reported prolonged use without re-evaluation in nearly 40% of patients [12]. Our findings are consistent with such trends, suggesting a need for structured prescription review and patient follow-up.

Community pharmacists have a well-recognised role in ensuring safe and rational opioid use. Several interventional studies have demonstrated the positive impact of pharmacist-led opioid stewardship programs. Bell *et al.* conducted a systematic review showing that pharmacist interventions, such as medication therapy management, patient education, and prescriber communication, significantly reduced inappropriate opioid use and improved adherence to pain management guidelines [13]. Similarly, Moulsdale *et al.* found that integrating pharmacist alerts in pharmacy dispensing software led to a 35% reduction in high-risk tramadol–SSRI co-prescriptions in community situations. Our results underscore similar implications: implementing pharmacist-based alert systems and continuous education can substantially minimise DDI-related harm [14].

An additional apprehension identified in our study was the lack of documentation regarding patient counselling on potential DDIs and side effects. Counselling rates were suboptimal, mirroring findings by Jokanovic *et al.*, who noted that medication review and patient education remain underutilised in community pharmacies, particularly in low-resource settings. Strengthening pharmacist–patient interaction could therefore play a vital role in improving the safe use of weak opioids [15].

The prevalence of clinically significant DDIs involving CYP2D6 inhibitors, such as fluoxetine, paroxetine, and quinidine, was also noteworthy. Inhibition of CYP2D6 can decrease codeine's conversion to morphine, leading to reduced analgesia, or equally, enhance tramadol's serotonergic toxicity. Stamer *et al.* found that 10–15% of patients may experience inadequate analgesia due to CYP2D6 inhibition or genetic polymorphisms. These data reinforce the importance of both pharmacogenomic awareness and medication reconciliation at the pharmacy level [16].

Taken together, our study emphasises the need for continuous professional education, clinical decision support tools, and policy frameworks supporting pharmacist-led opioid surveillance in the community. Integration of electronic prescribing systems with automatic DDI alerts and pharmacist verification steps could effectively reduce the incidence of high-risk

combinations. In addition, public education on the dangers of self-medication with over-the-counter preparations containing codeine or tramadol is essential, as a recent cross-sectional survey by Odsuren *et al.* found widespread misuse of OTC codeine in developing regions [17].

CONCLUSIONS

The study concluded that safety, effectiveness, and adherence improved with the optimized therapeutic approach. The incidence of NMOs and DRPs decreased, particularly in safety-related NMOs, where both quantitative and non-quantitative unsafety were reduced, and efficacy improved. DRP categories, including interactions and adverse effect probability, highlight high-risk medications and help mitigate potential risks. Certain factors, such as treatment impairments and minimal alterations, indicate the need for therapy adjustments. Combinations of opioids with antidepressants, benzodiazepines, or anti-epileptics were associated with higher rates of DRPs and NMOs, increasing polypharmacy risks. Constipation, mental confusion, and falls emerged as the most significant predictors of poor outcomes.

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