Original Article

JHSMR Journal of Health Science and Medical Research

Effectiveness of Pharmacist-led Intervention on Physicians Prescribing for Outpatients in Vietnam: A Before- and After-intervention Study

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Received 6 August 2023 ● Revised 18 September 2023 ● Accepted 19 September 2023 ● Published online 21 February 2024

Abstract:

Objective: Drug-related problems (DRPs) can lead to treatment failures and high risks of hospitalization. This study aimed to evaluate the effect of pharmacist-led interventions on DRPs in outpatient prescribing and to determine the risk factors relative to these DRPs.

Material and Methods: A prospective study was conducted that compared before- (April 1 to June 30, 2020) and after- (June 1 to June 15, 2021) interventions on the outpatient prescribing process from a public hospital in Vietnam. The PCNE classification version 9.1 and suitable drug information were used to determine DRPs, which then used Drugs.com to find drug-drug interactions for each prescription. Collaborated with hospital pharmacists via reporting on the pre-intervention results, sending information sheets, and reminding doctors of the DRPs was conducted.

Results: 32.8% of prescriptions had at least 1 DRP in 500 pre-intervention prescriptions. In 500 post-intervention prescriptions, the proportion of at least 1 DRP prescription decreased from 32.8% to 31.0% (p-value>0.05). Prescriptions with ≥5 drugs increased the possibility of a DRP appearance (p-value<0.001).

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J Health Sci Med Res 2024;42(4):e20241038
doi: 10.31584/jhsmr.20241038
www.jhsmr.org

Conclusion: This intervention method was not thorough, so it was ineffective in reducing DRPs on outpatient prescriptions. It is necessary to conduct specific interventions on each DRP and more time to discuss with doctors to improve the effectiveness of prescribing.

Keywords: drug-related problem, outpatients, pharmacist, prescriptions, Vietnam

Introduction

Medications play an active role in relieving and curing disease conditions. However, inappropriate prescribing could lead to drug-related problems that increase the risk of side effects, drug interactions, and pressure on health insurance companies. A drug-related problem (DRP) is an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes[1]. According to the PCNE classification for DRPs V9.1, DRPs include: problems (treatment effectiveness and treatment safety), causes (drug selection, drug form, dose selection, treatment duration, dispensing, drug use process, patient-related and patient transfer related), planned interventions (no intervention, at prescriber level, at patient level, or drug level), intervention acceptance (intervention acceptance or intervention not acceptance), status of the DRP (problem status unknown, problem solved, problem partially solved and problem not solved)[1]. In Ethiopia (2021), a study showed that up to 71.5% of patients had drug-related problems[2]. A similar study in Vietnam (2022) found that approximately 88.8% of prescriptions had at least 1 DRP[3]. The usual occurrence of DRPs affects the quality of life, increased morbidity, and mortality[4].

Currently, pharmacist-led intervention in DRPs has been proven through many studies[3,5]. The research of Nguyen et al. (2022) also found that the number of DRPs in outpatients in Vietnam decreased after the intervention of a clinical pharmacist[3]. By checking prescriptions regularly, one can identify and prevent DRPs, avoid financial loss, and add immeasurable value to patient safety[6,7]. In Vietnam, the prescribing of drugs still has many inadequacies and unreasonableness due to redundant drug prescribing, abuse of antibiotics, injections, and vitamins, and lack of instructions on drug use for patients[8]. In addition to the measures of the Vietnam Ministry of Health, more studies are needed to assess the current situation properly and propose appropriate measures to support doctors in treating these diseases. Therefore, this study was conducted to evaluate the effects of clinical pharmacy interventions on DRPs in outpatient prescribing at a hospital in Vietnam and to determine the relative factors to the appearance of DRPs.

Material and Methods

Study design

A prospective study was conducted with before-and after-intervention.

Participants

Outpatient prescriptions were collected from the hospital's prescribing database at a public hospital in Vietnam from April 1, 2020, to June 30, 2020 (pre-intervention) and June 1, 2021, to June 15, 2021 (post-intervention).

Inclusion criteria

Selected prescriptions from patients aged 18 or older that came to the outpatient department (clinics: cardiology, general internal medicine, neuro-endocrinology, general internal medicine- dermatology-rheumatology, internal gastrointestinal-liver, general surgery, neurosurgery, surgical trauma) were collected.

Exclusion criteria

Prescriptions from pediatric departments, obstetrics departments, intensive care units, and oriental medicine clinics containing traditional medicines, the same patients coming for follow-up visits during this period, and prescription software errors missing information were excluded.

Intervention

The intervention was conducted within two weeks. In the first week, collaboration was undertaken with the hospital's clinical pharmacists to discuss pre-intervention DRP outcomes and remedies for all doctors who prescribed outpatients. The research team reported 1-2 times (for about an hour) in briefing meetings during the intervention, a common method used in Vietnam, and made the second report mainly for doctors absent from the first intervention report. In each briefing meeting, A PowerPoint presentation to report DRPs was used, with questions answered and feedback taken from doctors during the meeting.

At that point, the doctors were provided with information sheets regarding DRPs, common drugs in DRPs, and directions to overcome each type of DRP; according to the summary of product characteristics, This was taken from the Vietnamese National Drug Formulary 2018 and the diagnosis and treatment guidelines of the Vietnam Ministry of Health[21,22].

The research team exchanged all feedback and suggestions from doctors trained in DRPs through the chat group on Zalo; additionally, the doctors could ask or call the research team directly. The research team's clinical pharmacists would discuss DRPs that frequently occurred with specific doctors when prescribing outpatient drugs.

DRP measurements

Clinical pharmacists identified DRPs, based on the PCNE classification system version 9.1, and used the information about these drugs, including a summary of product characteristics, Vietnamese National Drug Formulary 2018[1,20]; information on disease and treatment instructions: the hospital's treatment protocol (if any), the diagnosis and treatment guidelines of the Vietnam Ministry of Health (updated at the website https://kcb.vn/)[21]. Drug-drug interactions from Drug.com were then reviewed[22]. DRPs included:

(1) DRPs on drug selection: inappropriate drugs; according to guidelines/formulary; no indication for drugs; no or incomplete drug treatment, despite existing indication.

(2) DRPs on dose selection: drug dose too low; drug dose of a single active ingredient too high.

(3) DRPs on dosage regimen: dosage regimen not frequent enough; dosage regimen too frequent

(4) DRPs on dose timing instructions are wrong, unclear, or missing.

(5) Other causes; specify: time of taking medications relative to meals; major interactions (major drug-drug interaction only; according to Drugs.com)[22].

Risk factors related to the occurrence of DRPs, expected to be included in the analysis, included pharmacist's intervention, patient characteristics (age, gender), and prescription characteristics (total drugs or total diseases in a prescription).

Sample size

It was estimated that the number of prescriptions for the study, based on the sample size estimation formula in the population, with the rate of prescriptions having at least 1 DRP at a time, would be 0.89[3], with 95% confidence and a 2% error. A minimum sample size of 480 prescriptions was calculated; for which all prescriptions, in two similar stages, were collected using a simple random sampling method, equivalent to around 500 for evaluation.

Data analysis and processing

Data was analyzed using Microsoft Excel 2019 and IBM Statistical Package for the Social Science (SPSS)

Statistics 23.0 software. Qualitative variables were frequency and percentage; quantitative variables were described as mean±standard deviation. The general and individual DRP evaluation criteria were evaluated by statistical tests, with a 95% confidence interval (CI) to measure the difference in the presence of pharmacists' intervention, wherein the comparison of two proportions used the Chi-square test or Fisher test (when more than 20% of the cells in the comparison table had an expected value <5), whilst the comparison of two mean values for two independent samples used the test Independent-Sample T-test for normally distributed quantitative variables or the Mann-Whitney U test for non-normally distributed quantitative variables. Multivariable logistic regression was applied to check the relevance between the occurrence of DRP and the population characteristics: the difference was statistically significant when the p-value<0.05.

Ethics in research

The study was approved by decision No. 42/HDDD-PCT of the Medical Ethics Council of Can Tho University of Medicine and Pharmacy on May 27, 2020, and accepted for commencement at the study hospital in Vietnam in 2020.

Results

In total, 500 pre-intervention and 500 post-intervention prescriptions were collected. Patient characteristics and the difference in patient characteristics pre- and post-intervention prescriptions are presented in Table 1.

The difference between prescriptions with at least 1 DRP before and after the intervention was insignificant (p-value>0.05). However, the different proportions of each DRP in pre- and post-intervention were statistically significant (p-value<0.05); including drug selection, dosage regimen not being frequent enough, and major interactions. After the intervention of the pharmacists, the ratio of DRPs tended to decrease, such as drug selection (12.8% dropping to 8.0%), time of taking medications relative to meals (12.2% dropping to 10.4%), and dose timing instructions wrong, unclear or missing (9.2% dropping to 8.2%). DRPs in pre- and post-intervention prescriptions are presented in Table 2.

The prescriptions with ≥5 drugs were more likely to appear as DRPs than the prescriptions with <5 drugs odds ratio (OR)=2.260; 95% CI: 1.661-3.074), with statistical significance (p-value<0.001). The risk factors associated with the occurrence of DRPs are presented in Table 3.

Discussion

At least one DRP

It was determined that 32.8% of prescriptions had at least 1 DRP in the pre-intervention stage. This rate was lower than in some studies in Vietnam, such as Truong et al. (2020); wherein the prevalence of DRPs was 61.1%[18]; and in the case of Nguyen et al. (2022), 88.8% of prescriptions with at least 1 DRP[3]. This rate was also lower than the results of some studies globally[10-12]. The cause of this difference could be due to specific research populations, such as hypertensive patients using antimicrobial therapy as outpatients or older inpatients who received an average of 11 drugs per prescription[11,12]. Additionally, this study determined DRPs using the PCNE classification system version 9.1, while the other studies used the PCNE classification system version 6.02 or versions 7.0[10,12]. Another study, which recorded a lower proportion of these DRPs than this, was study conducted in a cardiology ambulatory care in Saudi Arabia[13].

This study's results showed a decrease in prescriptions having at least 1 DRP after intervention (32.8% dropping to 31.0%). This slight reduction could indicate that physicians were generally interested in certain prescribing DRPs. This trend was also observed in specific research populations, such as inpatients with cardiovascular diseases aged 35 years and older, in the study of Sagita

Table 1 Patient characteristics in pre-and post-intervention prescriptions

Characteristics		Pre-intervention (N=500)		Post-intervention (N=500)		p-value
		n	%	n	%	
Gender	Female	290	58.0	270	54.0	0.203
	Male	210	42.0	230	46.0	
Age (years)	Mean±S.D.	57.6±15.2		58.5±14.0		0.290*
	<60	269	53.8	250	50.0	
	≥60	231	46.2	250	50.0	
Total diseases in a prescription	Mean±S.D.	2.9±1.8		3.9±2.1		**<0.001***
	≤2	247	49.4	152	30.4	
	>2	253	50.6	348	69.6	
Total drugs in a prescription	Mean±S.D.	3.6±1.9		4.0±2.2		**0.013***
	<5	343	68.6	322	64.4	
	≥5	157	31.4	178	35.6	

n=number, p-value=probability value, *Using T-test to compare mean and chi-square test to compare percentages

Table 2 DRPs in pre-and post-intervention prescriptions

Code v9.1	DRPs	Pre-intervention (N=500)		Post-intervention (N=500)		p-value*
		n	%	n	%	
	At least one DRP	164	32.8	155	31.0	0.541
C1	**Drug selection**	64	12.8	40	8.0	**0.012**
C1.1	Inappropriate drug according to guidelines/ formulary	18	3.6	0	0.0	**<0.001**
C1.2	No indication of drug	42	8.4	3	0.6	**<0.001**
C1.5	No or incomplete drug treatment despite existing indication	6	1.2	38	7.6	**<0.001**
C3	**Dose selection**	13	2.6	16	3.2	0.457
C3.1	Drug dose too low	8	1.6	13	2.6	0.207
C3.2	Drug dose of a single active ingredient too high	5	1.0	4	0.8	0.801
–	**Dosage regimen**	15	3.0	16	3.2	0.723
C3.3	Dosage regimen not frequent enough	4	0.8	13	2.6	**0.018**
C3.4	Dosage regimen too frequent	11	2.2	4	0.8	0.082
C3.5	**Are timing instructions wrong, unclear, or missing**	46	9.2	41	8.2	0.749
C9.2	**Time of taking medications relative to meals**	61	12.2	52	10.4	0.496
	Major interaction	19	3.8	26	5.2	**0.028**

DRPs=drug-related problems, Bold values are the sum proportion of each category, *Using chi-square test to compare percentages

Table 3 Risk factors associated with the occurrence of DRPs

Characteristics*		n	DRPs		OR	95%CI	p-value
			No (%)	Yes (%)			
Intervention	No (Pre-stage)	500	336 (67.2)	164 (32.8)	1	-	-
	Yes (Post-stage)	500	345 (69.0)	155 (31.0)	0.896	0.680-1.181	0.435
Gender	Male	440	300 (68.2)	140 (31.8)	1	-	-
	Female	560	381 (68.0)	179 (32.0)	1.049	0.797-1.380	0.734
Age Age (years)	<60	519	365 (70.3)	154 (29.7)	1	-	-
	≥60	481	316 (65.7)	165 (34.3)	1.006	0.756-1.338	0.968
Total drugs in a prescription	<5	665	492 (74.0)	173 (26.0)	1	-	-
	≥5	335	189 (56.4)	146 (43.6)	**2.260**	1.661-3.074	**<0.001**
Total diseases in a prescription	≤2	399	282 (70.7)	117 (29.3)	1	-	-
	>2	601	399 (66.4)	202 (33.6)	1.053	0.777-1.426	0.741

DRPs=drug-related problems, OR=odds ratio, CI=confidence interval. *Using Binomial Logistic Regression: the variables entered were intervention, gender, age, patient's disease, and the number of drugs in a prescription. Five significant determinants are presented

et al. (2018)[14], which reduced both the number and types of DRPs; however, the occurrence of DRPs at each stage was independent (p-value>0.05). This result differs from similar studies (p-value<0.01) and differences in intervention forms between studies on specific patient populations[14-16].

The incomplete process of intervention could affect this study's results. First, physicians rotate shifts in the clinic. The report and information-access process (DRP pre-intervention result sheets) were only done with the doctors working at this time, so the exchange time between the research was limited, especially for the new doctors. Second, the physicians may not have clarification on the clinical importance of DRPs (not yet evaluated) because the consequences of these DRPs on the patient's health status may not have been considered. Third, an intervention was not performed on each specific issue with each doctor, and they had not been in contact with patients to record more information, so the effectiveness of the intervention may not be high.

The authors should discuss the results and how they can be interpreted from the perspective of previous studies and the working hypotheses. The findings and their implications should be discussed in the broadest context possible; future research directions should also be highlighted.

Drug selection

DRP on drug selection (12.8%) was the most frequent DRP in the pre-intervention phase. This DRP could be related to certain classes of drugs prescribed in this hospital, or this study used a newer and more detailed DRP classification (PCNE v9.1), so the rate was high. No

indications for drugs (8.4%) were usually related to analgesic and gastrointestinal drugs. According to the guidelines/formulary (3.6%), inappropriate drugs accounted for the second major problem; the cause of this could be that physicians may have weighed the benefits against the risks in treating patients. The last one was a no or incomplete drug treatment, despite existing indication (1.2%); these drugs were often related to cardiovascular diseases, chronic diseases, or geriatric diseases; it could be that patients still had drugs to treat these diseases (or bought them on their own), so the doctor did not prescribe more to avoid duplicate drugs.

Of all DRPs, the DRPs on drug selection showed the effectiveness of the pharmacist-led intervention. The proportions of DRP indications generally decreased after the intervention (12.8% dropping to 8.0%), and the difference between the two periods was statistically significant (p-value<0.05). Similar results were observed in a study evaluating clinical pharmacist interventions on clinical and drug-related problems in general hospital coronary inpatients in Indonesia (2018), wherein indications for non-optimal drugs decreased (from 37.5% to 4.5%, p-value<0.05)[14].

Among them, inappropriate drugs, according to the guidelines/formulary (3.6% to 0.0%) and no indication for drugs (8.4% to 0.6%), were the most concerning DRPs for doctors, which had significant decreases. Doctors were very interested in two issues when prescribing drugs, as DRPs often cause serious drug-drug interactions. In contrast, treatments that included many common drugs in chronic diseases could directly affect patients. However, despite existing indications, DRP on no or incomplete drug treatment (1.2% increased to 7.6%) showed a drug deficiency in prescribing to patients with more diseases (the mean conditions were 2.9 in pre- and 3.9 in the post-phase). This study's research method did not directly contact the patients to collect information, so it was impossible to specifically evaluate why the doctor did not prescribe the drugs excluded.

Dose selection and dosage regimen

In the pre-intervention phase, DRPs on the dosage regimen (3.0%) and dose selection (2.6%) were the least frequent DRPs. DRPs on the frequency of use due to doctor's prescribing habits usually defaulted to drugs used twice a day. In contrast, some drugs (itopride, rebamipide, etc.) recommend usage 3 times per day or only once daily (bisoprolol, etc.). An inappropriate dosage regimen of use could also lead to inappropriate dosing. DRPs on a low dose and high frequency of administration were common in gastrointestinal medications, especially proton pump inhibitors (PPIs). For example, PPIs in the prevention of gastric and duodenal ulcers are associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at significant risks: omeprazole (or esomeprazole) at a dose of 20 mg once daily (or esomeprazole 20 to 40 mg once daily) is recommended, so that any other dose would be defined as DRPs.

After the pharmacist's intervention, the results recorded DRPs at the dose selection (2.6% to 3.2%) and dosage regimen (3.0% to 3.2%), which tended to increase after the intervention. In particular, the proportion of DRP drug doses that were too low was increased (1.6% to 2.6%). Doctors considered dosage when prescribing and chose low doses for their patients. The doctor's mentality was that of being afraid of overprescribing. Additionally, the doctors did not pay attention to the dose and did not update the drug information: the proportion of DRP's dosage regimens not being frequent enough increased (from 0.8% to 2.6%). Doctors reduced the frequency of use to make it easier for patients. They always prescribed drugs twice a day, as usual, and forgot this DRP. It is necessary to evaluate the

impact of DRPs on a case-by-case basis to determine the severity of the impact on the course of treatment in the following studies.

Do timing instructions wrong, unclear, or missing, and time of taking medications relative to meals

In the pre-intervention stage, the dose timing instructions were wrong, unclear, or missing (9.2%), and the time of taking medications relative to meals (12.2%) were common DRPs. They were often overlooked when prescribing and could influence the effectiveness of treatment from a pharmacokinetic perspective. The dose timing of a day for many drugs (such as bisoprolol, felodipine, etc.) is relatively easy to remember and usually pre-installed on the hospital's prescribing database. Hence, doctors are often subjective about this issue. Taking drugs relative to meals is more difficult to remember, especially since DRP often appears in PPIs and diabetes medicines. PPIs should be taken 30 minutes before breakfast (once-daily dosing regimens) or before meals (twice-daily dosing regimens). The intake of these before or after meals also contributes to a change in the effectiveness of treatment. Metformin should be taken with or shortly after a meal because taking it on an empty stomach can cause more gastrointestinal side effects (nausea, vomiting, abdominal pain, and diarrhea).

These DRPs were of more concern by the physicians after the intervention, which showed a decrease in occurrent proportions (the dose timing instructions wrong, unclear, or missing decreased from 9.2% to 8.2%, and the time relative to meals decreased from 12.2% to 10.4%). Each DRP differed independently between the two stages (p-value>0.05). This decrease in DRPs was not due to a pharmacist-led intervention. Rather, it was caused by using some typical drugs that are commonly used in hospital treatment protocols, wherein this accounted for the majority of the total number of DRPs of prescriptions. Although the extent of the influence of these DRPs has not been documented in this study, for ensuring optimal treatment effectiveness for patients, other forms of information or more specific reminders are needed by physicians to limit these DRPs.

Drug interaction

The proportion of DRP major drug-drug interactions accounted for 3.8% in the pre-intervention period. The research's most common major interaction pairs were between opioids (mainly tramadol) and gabapentinoids (pregabalin or gabapentin). For warning purposes, concurrent use is not recommended in medication leaflets, so choosing an alternative analgesic for patients treated with gabapentinoids may also be an appropriate solution.

After the intervention, the recorded results consisted of a rise in major drug interactions (from 3.8% to 5.2%); this difference was statistically significant (p-value<0.05). The major drug-drug interactions (according to Drugs.com) that were seen were mostly managed with close monitoring: only a few cases recommended contraindication combinations (clarithromycin+methylprednisolone, levofloxacin+methylprednisolone, etc.). Specifically, it was found that the pair of interactions with clarithromycin and methylprednisone no longer existed after the intervention (100% reduction). In contrast, the spironolactone+valsartan interaction pair did not improve. Doctors only focused on treating diseases and did not pay attention to major interactions, or they considered the benefits and risks, and then they made a plan to monitor drug interactions. The hospital did not install any programs to recognize interactions on their computer systems.

To reduce the proportion of DRPs, pharmacists should consider more interventions, such as talking to doctors, finding out the doctors' difficulty in prescribing,

providing more drug information, and reporting notes during briefing meetings within the hospital. Pharmacists should ask the hospital to install interaction programs and update major interactions with each doctor. Moreover, the pharmacy faculty should organize seminars to update DRP information and tests after such seminars.

As well as leading to more DRPs in dose and frequency of administration than before the intervention, the majority of prescriptions with ≥5 drugs and patients with >2 diseases at the post-intervention stage were seen. A study in Hau Giang, Vietnam, showed that the higher the number of drugs used in the prescription, the higher the rate of drug interactions occurring in outpatient prescriptions[17]. Similarly, a study in Can Tho, Vietnam, also showed that using ≥5 drugs in the prescription increased drug interactions[18]. On the other hand, each doctor was not contacted to intervene more closely.

Risk factors associated with the occurrence of DRPs

The results show that the number of drugs in the prescription is a factor that affects the occurrence of DRPs, with statistical significance (p-value<0.001). Specifically, prescriptions with ≥5 drugs had a higher risk of DRPs than prescriptions in the same comparison group (OR=2.260; p-value<0.001). This is related to the increased DRP proportions, such as dose, frequency of use, and major interaction.

The assessment of DRPs was based on three documents referenced by health insurance to pay expenses. This is a very important factor. Because most of the patients in this study had health insurance at the hospital, inappropriate cases will lead to out-of-pocket payments affecting hospital funding. This study used the PCNE v9.1 DRP classification system, a popular DRP classification system globally, and included possible interventions that are relatively easy to implement within the hospital[1]. Clinically, this study could be applied at the hospital and supported by doctors during the effective period of circular 30/2018/TT-BYT. This is a circular of the Vietnam Ministry of Health concerning the promulgation on the list of modern medicines, biologicals, radiopharmaceuticals, and tracers covered by health insurance; insurance coverage ratio and payment conditions: having taken effect as of January 1, 2019[20]. If the research is widely applied, it can improve treatment effectiveness, safety, and costs for outpatients. In terms of science, this study initially opens up many further research directions to deepen and evaluate the impact of DRPs on clinical practice or for the commencement of appropriate interventions for each specific case of DRP.

Limitations

This study's sample size was small (500 prescriptions in each stage). It is recommended to investigate more prescriptions of patients examined by fee-for-service short sampling time (3 months). Therefore, sampling would cover about one year to cover local disease patterns and the statistical system. The hospital prescription database was incomplete during the COVID-19 epidemic; therefore, there was no communication with the patients, a shortcoming made the review of DRP criteria somewhat vague. The rotating mechanism within the clinic could also have influenced the effects of interventions in this study. Acknowledging the above limits is the basis for overcoming and implementing further studies and pharmaceutical practices.

Conclusion

In this study, the pharmacist-led intervention was not thorough, so it was ineffective in reducing DRPs on outpatient prescriptions. Prescriptions with ≥5 drugs were more likely to occur as DRPs than prescriptions in the same comparison group. Clinically, the intervention in this

study was feasible and relatively easy to implement within the hospital. Scientifically, this study initially opens up many further research directions to evaluate the impact of DRPs on clinical and appropriate interventions for each case.

Acknowledgement

We thank you for the support from the study hospital, the Department of Science and Technology of Ben Tre, the Department of Health of Ben Tre, and Can Tho University of Medicine and Pharmacy in Vietnam.

Conflict of interest

There are no potential conflicts of interest to declare.

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