

The Difference in Contributing Factors and Costs Associated with Outpatient Refusal to Accept Cardiovascular Medications or Analgesics During Dispensing Process.

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Abstract

Activities during dispensing process is vital in reducing antihypertensive and analgesics waste. However, study looking into refusal to accept cardiovascular disorders (CVD) medicines or analgesics activities during dispensing process is lacking.

To determine differences in factors and costs associated with refused CVD medicines or analgesics during dispensing process

This study was approved by Medical Research and Ethics Committee (MREC) (Registration number: NMRR-20-177-53153(IIR)). Participants receiving CVD medicines or analgesics during dispensing process were recruited via convenience sampling technique between February and March 2020 at the Outpatient Pharmacy Department of Jerantut Hospital, Malaysia. Refusal to medications and its reasons were asked based on the questionnaire developed by the researchers.

Overall, 175 patients participated in this survey and CVD drugs contributed toward 58.9% of the refused medicines. Those who refused CVD drugs and analgesics were significantly different in terms of gender, medications dosing frequency, refusal reasons namely side effects, medications use, intentionally skipping dose and skipping the dose when feeling well. No associations were found between forgetfulness and age with refusal to CVD drugs or analgesics. Those who refused CVD medicines had a significantly higher total daily medicines, total daily pill burden, and total number of medicines refused per prescription compared to those who refused analgesics. Cost of CVD medicines refused per prescription was significantly higher compared to analgesics, median United States Dollar (USD) 2.58 (IQR, USD 3.69) versus median USD 1.47 (IQR, USD 3.69), P=0.01.

Refusal to CVD medicines and analgesics was associated with several medication's and patient's factors. However, higher cost of refused medication was observed for CVD medicines.

Keywords: Cardiovascular disease, Analgesics, Dispensing, Wastage

Introduction

Today, healthcare system around the globe is burdened with increasing healthcare cost due to struggling economy and the responsibility to provide accessible medical care to the populations.^(1,2) Despite this, occurrence of medication wastage is still at large. For instance, Arabian Gulf Countries reported USD 150 million worth of medications were wasted annually in that region alone⁽³⁾.

Usually, various factors could contribute toward medication waste such as patients' poor medication adherence and change in medical regime⁽²⁾. Other possible factors include oversupply of medication due to lack of interactions between pharmacists and the patients during dispensing process.¹ This can occur under certain scenarios such as patients are continued to be dispensed with *pro re nata* (PRN) drugs such as analgesics by the pharmacists even though these patients are not using them⁽⁴⁾.

In order to reduce drug wastage, a more proactive steps should be taken by the pharmacists at various stages of medication supply. For instance, pharmacists can play a role during prescribing

process by giving advice and recommendation related to polypharmacy intervention⁴ and de-prescribing of inappropriate medicines to the prescribers⁽⁵⁾. Another step to reduce medication waste involves discussion between pharmacists and their patients regarding the quantities of medication needed during dispensing process, so that patients would not keep excess medication at home⁽⁶⁾. Effective communication during the dispensing process is vital since research has shown that pharmacists strongly believe that activities undertaken during dispensing process is crucial in reducing medication waste⁽⁶⁾. Once the medications are released to the patients, the only initiatives to reduce medication waste involves collection of unused drug by the pharmacists for re-use⁽¹⁾. However, pharmacists believed that activities involving re-dispensing unused medications returned by patients as the least importance stage and impractical in medication waste reduction process⁽⁶⁾.

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This is due to the fact that only around 25% of returned medications were usually eligible for re-dispensing⁽⁷⁾.

There are also issues involving safety, appropriateness and cost effectiveness related to this practice⁽¹⁾. Previous studies reported that the trends in the quantity of medication wasted or returned unused to the pharmacies varied across different countries. For example, research in Taiwan², United Kingdom⁽⁷⁾ and the United States⁽⁸⁾ reported higher cardiovascular disease (CVD) drugs wasted compared to musculoskeletal disorder drugs. On the contrary, quantities of musculoskeletal disorder drugs wasted were higher compared to CVD drugs in Austria⁽⁹⁾, Malta⁽¹⁰⁾ and another part of the United States⁽¹¹⁾.

Generally, available studies focused mainly on amount and cost of drugs returned to or disposed by pharmacies^(2,7,8,9,10) and factors associated with unused drugs such as improved health conditions, forgetfulness, medication's side effects^(2,11). Other research have also looked into the cost saving activities involving polypharmacy interventions⁽⁴⁾ and de-prescribing medications during prescribing stage^(4,5). Study has shown that 55% and 10% of de-prescribed drugs in patients prone to fall were contributed by CVD drugs and tramadol analgesics respectively⁽¹²⁾.

CVD drugs and analgesics are of particular interest to the current setting since we have observed that CVD drugs and analgesics are commonly refused or rejected by the patients during dispensing process. In addition, CVD drugs were commonly returned unused to our pharmacy. However, there is paucity in the studies that investigate the involvement of factors associated with refusal to CVD drug. Thus, this study aimed 1) to determine differences in factors associated with outpatient refusal to some dispensed cardiovascular disorders (CVD) medicines or analgesics and 2) to measure the cost difference between CVD drugs or analgesics refused by patients during dispensing process.

Method

This cross-sectional study was conducted during dispensing process using convenience sampling method at Outpatient Pharmacy Department of Jerantut Hospital, Malaysia from February to March 2020. This is a public health facility and the cost for the medications are provided free of charge by the government of Malaysia. This study was approved by Medical Research and Ethics Committee (MREC) (Registration number: NMRR-20-177-53153(IIR)).

This study involved patients who collected CVD medications or prescription-only analgesics at our outpatient Pharmacy Department. Data collection involved several steps that was agreed between researchers prior to the initiation of the study. The principal and co-investigators have

working experience of 12 years and one year respectively. Data collection by the co-investigators are supervised by the principal investigator During the dispensing process, medications were dispensed to the patients by the researchers according to the current facility standard operating procedure. Researchers also provided counselling related to the importance of medication adherence, health complications that arises due to medication non-adherence for their specific conditions, medications side effects, medication administration, storage of medication and how to examine medication expiry dates. As part of an initiative to reduce medication wastage during dispensing process^(1,6), patients were also enquired if they kept excess stock of medications at home. If they did, they were advised to finish remaining medication at home before opening the recent medication supply. Finally, patients were also informed regarding the study and invited to participate. After signing the consent form, participants were enquired if there were any of the previously dispensed medications that they wished to refuse. Medication refusal referred to patient's act of rejecting medications at the dispensing counter before the end of the dispensing process. Researchers would also enter the participants' details such as gender, age, name of medications refused, total daily medicine (TDM) and total daily pill burdens (TDPB) into the data collection form. The participants were also asked to choose the reasons for their medication refusal. These questions were developed by the researchers based on the factors associated with medication waste reported from the previous research.^(2,11) Participants were asked if 1) they experienced any medication's side effects, 2) they felt that they did not need the medication, 3) they ever forget to take the dose prescribed and 4) they intentionally missed the dose prescribed and 5) they ever skipped the dose when they felt well. The TDM referred to count of different oral medications prescribed to patients⁽¹³⁾. The TDPB referred to total number of pills patients had to consume on daily basis⁽¹³⁾. For PRN oral medications, its pill burden was estimated from the pharmacy information system (PhIS). This is an online prescription system that stores patients' medication details and the price for the drugs used at current facility.

Percentage of medicines refused during dispensing process referred to the total numbers of medicines refused per total numbers of medicines prescribed on the same prescription. Regularly dosed drugs referred to drugs that were prescribed to be taken regularly on daily basis by the prescribers⁽¹⁴⁾. PRN dosing referred to drugs that were prescribed to be taken as required or when necessary⁽¹⁴⁾.

Medications refused by the participants were grouped accordingly for data analysis. Cardiovascular medications refer to combinations of any type of antihypertensive (calcium channel

blockers (CCB), beta blockers (BB), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), diuretics, alpha blockers) and anti-anginal drugs (glyceryl trinitrate (GTN), trimetazidine and isosorbide dinitrate, antiplatelet (aspirin, clopidogrel) and anti-hypercholesterolemia (simvastatin, atorvastatin, pravastatin, gemfibrozil, fenofibrate))⁽⁵⁾. Analgesics include prescription-only drugs from nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib or meloxicam and/ or opioids tramadol that are available at current facility. Total cost for every prescription and price for every item refused was generated from the PhIS. Inclusion criteria of this study were: all patients who refused the prescribed CVD medications or prescription-only analgesics (oral celecoxib or oral meloxicam and/or oral tramadol) during dispensing process, aged more than 18 years old and collected medication by themselves. Exclusion criteria were patients from emergency department, newly started on CVD medicines or prescription-only analgesics treatment on the day of the data collection and did not refuse the prescribed CVD medicines or prescription-only analgesics. Statistical Package for Social Sciences (SPSS) version 21.0 was used for the statistical analysis. Mann Whitney U test and Chi-Square test were used for continuous and categorical variables respectively. Continuous variables were expressed as median with interquartile range (IQR) where applicable. A $P < 0.05$ was considered statistically significant.

Result

Between February and March 2020, 175 patients agreed to participate in this survey. Most of the participants were male, 56% (n=98). Median age of the participants were 62.0 years old (IQR, 15.0). The medians TDM and TDPB for the participants were 6.0 (IQR,4.0) and 7.0 (IQR, 6.0) respectively. The medians for treatment cost was USD 17.69 (IQR,USD 19.41). Medians number and the percentage of medicines refused per prescription during dispensing process were 1.0 (IQR, 1.0) and 20.0% (IQR, 19.1%) respectively. Medians for cost of medicine refused during dispensing process per prescription was USD 2.13 (IQR,USD 3.48). CVD drugs and analgesics contributed toward 58.9% (n=103) and 41.1% (n=72) of the refused medicines respectively. The most commonly refused CVD drugs were calcium channel blockers group, 28.2% (n=29). For analgesics, 76.4% of the refused drugs were tramadol (n=55). Data are shown on table 1.

Table 1. Demographic and treatment characteristics

Parameter	Median (IQR)
Age (years)	62 (15.0)
Total daily medicines	6.0 (4.0)
Total daily pill burden	7.0 (6.0)
Treatment cost (USD)	17.71(19.41)
Total medicines refused	1.0 (1.0)
Median percentage of medicines refused (%)	20.0 (19.1)
Cost of medicines refused (USD)	2.13 (3.48)
Percentages for cost of medicines refused (%)	13.9 (19.8)
Type of medicines refused (n, %)*	
Cardiovascular drugs	103 (58.9)
Analgesics	72 (41.1)
Groups of CVD drugs refused (n,%)*	
GTN	11 (10.7)
Calcium channel blockers	29 (28.2)
Beta blockers	21 (20.4)
Angiotensin converting enzyme inhibitors (ACEi)	5 (4.9)
Angiotensin II receptor blockers	6 (5.8)
Diuretics	6 (5.8)
Antihyperlipidemia	10 (9.7)
Antiangina	15 (14.6)
Groups of analgesics refused (n,%)*	
Tramadol	55 (76.4)
Nonsteroidal anti-inflammatory drugs	17 (23.6)
Data are expressed as median (IQR) except where indicated	
*Data are expressed (n,%)	

Age for the participants who refused CVD medicines was not significantly different compared to those who refused analgesics, median 69.0 years old (IQR, 19.0) versus median 63.5 years old (IQR, 14.0), $P=0.136$. However, refused CVD drugs were mostly contributed by male participants (67%) while refused analgesics were mostly contributed by female participants (59.7%), ($X^2=12.272$, $dF= 1$, $P<0.05$). Majority of the refused CVD drugs were prescribed as regular dosing (89.3%) while refused analgesics were mostly prescribed as a PRN dosing (59.7%), ($X^2=47.772$, $dF= 1$, $P<0.05$). Majority of the refused CVD drugs were due to side effects (82.5%) compared to only 18.1% of the refused analgesics, ($X^2=71.481$, $dF= 1$, $P<0.05$). However, most of the refused analgesics were due to 'does not need' (77.8%) compared to 27.2 % of the refused CVD drugs, ($X^2=43.458$, $dF= 1$, $P<0.05$). Forgetfulness to take the dose did not differ between

refused CVD drugs or analgesics, ($X^2=0.001$, $df=1$, $P=0.981$).

Majority of those prescribed with analgesics (76.4%) intentionally skipped their drug compared to those prescribed with CVD drugs (23.3%) ($X^2=48.228$, $df=1$, $P<0.05$). Around 86.1% of patients who were prescribed analgesics were associated with skipping the dose when feeling well compared to 12.6% of those were prescribed CVD drugs ($X^2=93.454$, $df=1$, $P<0.05$).

Patients who refused CVD medicines reported a significantly higher TDM compared to those who refused analgesics, median 7.0 (IQR, 3.0) versus median 4.0 (IQR, 3.0), $P<0.05$. Patients who refused CVD medicines also reported a significantly higher TDPB compared to those who refused analgesics, median 9.0 (IQR, 6.0) versus median 5.0 (IQR, 5.0),

$P<0.05$. Median treatment cost for participants who refused CVD medicines was USD 23.09 (IQR, USD18.92) versus USD 14.13 (IQR, USD14.49) for analgesics, $P<0.05$. Total number of CVD medicines refused per prescription was significantly higher compared to the total numbers of analgesics refused per prescription, median 1.0 (IQR, 1.0) versus median 1.0 (IQR, 0), $P<0.05$. However, percentage of CVD medicines refused per prescription was significantly lower compared to percentage of analgesics refused per prescription, median 20.0% (IQR, 10.7%) versus median 25.0% (IQR, 30.5%), $P<0.05$. The cost of CVD medicines refused per prescription was significantly higher compared to analgesics, median USD 2.58 (IQR, USD 3.69) versus median USD 1.47 (IQR, USD 3.69), $P=0.01$. Data are shown on table 2.

Table 2. Difference in factors and cost between refused CVD medications and analgesics

	CVD medicine	Analgesic	X^2	df	P-value
Age (years)	60.0 (19.0)	63.5 (14.0)			0.136
Gender (n,%) *					
Male	69 (67.0)	29 (40.3)	12.272	1	<0.05
Female	34 (33.0)	43 (59.7)			
Dosing (n, %)*					
Regular	92 (89.3)	29 (40.3)	47.772	1	<0.05
PRN	11 (10.7)	43 (59.7)			
Reasons for refusing					
Side effects (n, %)*					
Yes	85 (82.5)	13 (18.1)	71.481	1	<0.05
No	18 (17.5)	59 (81.9)			
Does not use the medicine (n, %)*					
Yes	28 (27.2)	56 (77.8)	43.458	1	<0.05
No	75 (72.8)	16 (22.2)			
Forgetfulness to take dose (n, %)*					
Yes	90 (87.4)	63 (87.5)	0.001	1	0.981
No	13 (12.6)	9 (12.5)			
Intentionally missed the dose (n, %)*					
Yes	24 (23.3)	55 (76.4)	48.228	1	<0.05
No	79 (76.7)	17 (23.6)			
Skipped dose when feeling well (n, %)*					
Yes	13 (12.6)	62 (86.1)	93.454	1	<0.05
No	90 (87.4)	10 (13.9)			
Total daily medicines	7.0 (3.0)	4.0 (3.0)			<0.05
Total daily pill burden	9.0 (6.0)	5.0 (5.0)			<0.05
Treatment cost (USD)	23.09 (18.92)	14.13 (14.49)			<0.05
Total numbers of medicines refused	1.0 (1.0)	1.0 (0)			<0.05
Percentage of medicines refused	20.0 (10.7)	25.0 (30.5)			<0.05
Cost of medicines refused (USD)	2.58 (3.69)	1.47 (3.69)			0.010
Percentage for cost of medicines refused	12.9 (18.3)	15.8 (22.0)			0.690
Data are expressed as median (IQR) except where indicated					
*Data are analysed using Chi-Square test					

Discussion

To our knowledge, this is the first study to compare refusal to CVD medicines and analgesics during the dispensing process. Current study recorded 58.9% medication refusal involving CVD medicines and this could be related to the fact that unused medicines returned to the pharmacies were commonly prescribed by cardiology division ⁽²⁾.

Factors associated with CVD drugs and analgesics refusal

Age

In current study, there was no association found between refused CVD medicines or analgesics with age. This finding is parallel with that of previous study that reported medication returned from various therapeutic groups was not associated with age.⁷ Similar to their study⁷, the age for the participants in our study who refused CVD drugs and analgesics were also revolved around those in their 60s. They also reported that the most commonly returned drugs were prescribed for CVD.

Gender

In current study, refusal to cardiovascular drugs were higher in male compared to females. This could be related to the fact that hypertensive males were less adherent to their medication compared to females due to factors such as busier lifestyle and heavier work pressure ⁽¹⁵⁾. Besides, females were more likely to make lifestyle changes and were more committed toward their hypertension management ⁽¹⁵⁾. On the contrary, relationships between analgesics' adherence ⁽¹⁶⁾ or consumptions ^(16,17,18) with gender varied across different studies. For instance, studies conducted in Norway ⁽¹⁷⁾ and Brazil ⁽¹⁸⁾ found that the use of non-prescription, over the counter (OTC) analgesics such as paracetamol, aspirin, ibuprofen ^(17,18) naproxen ⁽¹⁸⁾ and diclofenac ⁽¹⁸⁾ were significantly common in females. However, higher percentages of females refusing prescription-only analgesics in current study could be an indication of females' unwillingness to use these categories of analgesics.

Medication dosing

Most of the PRN medication prescribed in the care home (35.3%) came from analgesics groups.¹⁹ However, utilisation of prescription-only analgesics prescribed for PRN use in outpatient hospital setting might be minimal. This was reflected by the fact that 59.7% of analgesics refused in current study were prescribed for PRN use compared to only 10.7% of the CVD medicines. This finding was consistent with studies from Australia and the United Kingdom that reported, commonly returned PRN medicine for disposal by the community pharmacies were analgesics and GTN ^(7,24). Meanwhile, regularly dosed drugs such as statin, perindopril, telmisartan/amlodipine and frusemide were in the top 20s of the commonly returned unused to the pharmacy ⁽²⁴⁾.

Reasons for refusal

Apparently, majority of those participants who refused analgesics stated that they did not need the drugs prescribed, intentionally missed the dose and skipped the dose when feeling well. Current study indicates that discussion for the need of the prescribed analgesics between pharmacists and the patients has potential to minimize wastage since medications provided for occasional symptomatic relief such as acute pain or for conditions that have already resolved contributed toward 27.5% of unused medicines.² Current study also reported that, forgetfulness was common among those refusing CVD medicines or analgesics and was documented as one of the leading causes for medication being unused.¹¹ On the contrary, the discussion between pharmacists and the patients refilling their CVD medicines have uncovered that refusal to the CVD drugs might have stemmed from the side effects of the prescribed drugs.

TDM and TDPB

The occurrence of side effects or patient's unwillingness to take the prescribed drugs can be due to inappropriate polypharmacy ⁽⁴⁾. Apparently, patients who refused CVD medicines reported significantly higher total daily medicines (TDM) and total daily pill burden (TDPB) compared to those who refused the prescribed analgesics. Present of higher TDM also indicates occurrence of polypharmacy, defined as taking five or more medications per day ⁽²⁰⁾. Polypharmacy was associated with several side effects such as deterioration of renal function ⁽²³⁾ and orthostatic hypotension ⁽²²⁾. The high TDM of 7 among those prescribed with medication for CVD compared to only four in those prescribed with analgesics also posed as risk factors for medication wastage. This is because half of patients with TDM of only even four per day did not comply to their treatment regimen ⁽²³⁾. Besides, high TDPB were also commonly associated with poor medication adherence ⁽¹³⁾. This in turn results in excessive supply of medication at home and greater chances of medication wastage among those prescribed with chronic medication^(2,9,11).

Numbers and cost of medications refused

Polypharmacy intervention led by pharmacists has resulted in cost saving mostly via reduction of analgesics prescribed for PRN basis compared to their counterpart PRN CVD drugs ⁽¹⁴⁾. In contrast, enquiry of the needs for the dispensed drugs by the pharmacists during the dispensing process indicated that the drug's cost refused per prescription for CVD drugs was almost doubled of that refused analgesics. Possible explanation for this observation is that, our participants with CVD medicines refused between one to two drugs during dispensing process compared to only one type in those prescribed with analgesics. Nonetheless, the

high refusal to 20% of CVD medicines per prescription is a worrying observation. While polypharmacy intervention by pharmacists result in no reduction in the numbers of regularly dosed CVD⁽¹⁴⁾, yet majority of the refused CVD drugs in current study involved regularly dosed drugs. This indicates potential activities related to medication and behavioral interventions in order to minimize factors causing medication refusal or non-adherence in those prescribed with CVD medicines. On the other hand, refusal to 25% of analgesics per prescription indicates the need to assess the necessity of the prescribed analgesics in those diagnosed with musculoskeletal disorder. This is important in order to reduce unnecessary analgesics wastage at public sector hospital where medications are provided to the patients without any charges

Limitations

Firstly, medications collected by patients' representatives were excluded from the survey. Thus, refusal behavior and the cost associated with medication refusal might be slightly under- or overestimated. Secondly, recall bias during refusal might occur and resulted in patients refusing the medications they actually using or not using. Thirdly, medication adherence was not assessed. Thus the benefits of refusal toward reducing drugs wastage could not be confirmed. Fourthly, the balance of medication at home was not assessed hence the medication use behavior could not be assessed. Fifthly, while refusal to pick-up medicines may cause waste of income in addition to return to stock time if it occurs in private pharmacies, yet this effect was not investigated in this study since this study was conducted in governmental pharmacy where the medicines are subsidized. Finally, the study was conducted at our pharmacy alone. Hence the generalizability of the findings might be limited to our setting alone.

Conclusions

In conclusion, discussion on the refusal to CVD medicines or analgesics during dispensing process has uncovered several issues related to medication use in our patients. Refusal to these medications apparently were associated with several medications and patient's factors. Even though refusal to accept medication during dispensing process might prevent wastage, yet pharmacists have a responsibility to advise patients regarding issues related to side effects and other medication-related issues such as good adherence in those with CVD in order to prevent further health complications. In contrast, the needs for analgesics should be discussed for patients with musculoskeletal disorder since they might not always wish to refill it. This activity if conducted during dispensing process might have a potential to optimise medication use.

Conflict of Interests

The authors declared that they have no conflicts of interest to disclose.

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