การใช้ยาร่วมกันหลายขนานของผู้ป่วยสูงอายุที่รับการรักษาแผนกตรวจโรคผู้ป่วยนอกอายุรกรรม โรงพยาบาลรามาธิบดี

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บทคัดย่อ

การใช้ยาร่วมกันหลายขนานหรือการใช้ยาร่วมกันมากกว่าหรือเท่ากับห้าชนิดขึ้นไปซึ่งเป็นปัญหาที่พบได้บ่อยในผู้สูงอายุไทยส่งผลกระทบอย่างมากต่อภาวะทุพพลภาพและนำไปสู่การเสียชีวิต ดังนั้นวัตถุประสงค์การวิจัยสามารถบ่งชี้ ปัจจัยเสี่ยงและปัญหาอันเนื่องจากการใช้ยาที่มีความสัมพันธ์กับการใช้ยาร่วมกันหลายขนานเพื่อเพิ่มความตระหนักแก่บุคลากรทางการแพทย์ในการใช้ยาเพื่อนำไปสู่การป้องกันและลดการเกิดการใช้ยาร่วมกันหลายขนาน การศึกษานี้เป็นการศึกษาแบบ cross-sectional study ซึ่งมีการแบ่งกลุ่มผู้เข้าร่วมวิจัยออกเป็น 3 กลุ่มตามนิยามอันได้แก่กลุ่ม excessive polypharmacy (ยามากกว่า 9 ชนิด), polypharmacy (ยา 5-9 ชนิด) และ no polypharmacy (ยาน้อยกว่า 5 ชนิด) ผู้เข้าร่วมวิจัย 452 รายอายุมากกว่าเท่ากับ 60 ปีขึ้นไป เข้ารับบริการการรักษาแผนกตรวจโรคผู้ป่วยนอกอายุรกรรม โรงพยาบาลรามาธิบดี ตั้งแต่วันที่ 1 ธันวาคม พ.ศ. 2558 ถึง วันที่ 31 พฤษภาคม พ.ศ. 2559 ความชุกการใช้ยาร่วมกันหลายขนานประมาณ 74.8 เปอร์เซ็นต์ ซึ่งการวิเคราะห์ข้อมูลใช้ multivariate multinomial logistic regression analysis เพื่อค้นหาปัจจัยเสี่ยง โดยใช้กลุ่ม no polypharmacy เป็นกลุ่มอ้างอิงพบว่า โรคเบาหวานเป็นปัจจัยเสี่ยงอิสระที่มีความสัมพันธ์กับการใช้ยาร่วมกันหลายขนานมากที่สุด โดยมี (OR 3.61, 95% CI: 1.86-7.02; P < 0.001) จากการศึกษานี้พบว่าปัญหาอันเนื่องจากการใช้ยาที่สัมพันธ์กับการใช้ยาร่วมกันหลายขนานสามอันดับแรก ได้แก่ การเกิดปฏิกิริยาระหว่างยา (91.4%) ใช้ยาที่ไม่จำเป็นหรือไม่มีข้อบ่งชี้ (72.4%) และการใช้ยาไม่เหมาะสม (62.9%) ดังนั้นแพทย์ควรให้การตระหนักกับปัจจัยเสี่ยงเช่นเดียวกันกับการบริหารยาได้อย่างเหมาะสมเพื่อป้องกันการเกิดการใช้ยาร่วมกันหลายขนาน

คำสำคัญ: การใช้ยาร่วมกันหลายขนาน, ผู้สูงอายุ, ปัจจัยเสี่ยง, แผนกตรวจโรคผู้ป่วยนอก

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Polypharmacy among Older Adults in Outpatient Clinic, Internal Medicine Department, Ramathibodi Hospital

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Abstract

Polypharmacy or the concomitant use of five or more medications, which is one of the common problems among the elderly in Thailand, profoundly impacts on patients' morbidity and mortality. Therefore, the objective of this study is to determine related risk factors to polypharmacy and associated drug-related problems (DRPs) with polypharmacy in order to increase healthcare personnel's awareness, resulting in prevention and reduction of polypharmacy. This study was a cross-sectional study which the subjects were categorized into three groups based on definition such as the excessive polypharmacy group (>9 medications), the polypharmacy group (5-9 medications) and the no polypharmacy group (< 5 medications). Four hundred and fifty two recruited participants aged 60 years or over visited the Internal Medicine Outpatient Clinic of Ramathibodi Hospital, during the period from December 1st, 2015 to May 31st, 2016. The prevalence of polypharmacy was 74.8%. A multivariate multinomial logistic regression analysis to identify significant risk factors (no polypharmacy group as reference) revealed that odds ratio was presented strongest factor with the excessive polypharmacy group including diabetes mellitus (OR 3.61, 95% CI: 1.86-7.02; P < 0.001). Furthermore, the study revealed that three most common associated DRPs with polypharmacy were drug-drug interactions (DDIs) (91.4 %), unnecessary medications (72.4 %) and potentially inappropriate medications (PIMs) (62.9 %). Therefore, physicians should concern associated factors as well as appropriate drug administration to prevent polypharmacy.

Key words: Polypharmacy, The elderly, Risk factors, Outpatient clinic

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Introduction

In developing countries including Thailand, the elderly population has been rising since 2000. The Thai population of 60 years or older has risen markedly from 7.2 million in 2010 and is predicted to reach 11 million by 2020[1]. At the present, Thailand is coming into Aged Society which the population of older adults aged 60 or older is more than 20 % of total population. The elderly have increasing tendency of polypharmacy due to multiple comorbidities which were treated with concomitant medications. From previous study, the prevalence of polypharmacy in Thailand has varied, ranging from 29% to 36.8%[2,3]. The public health seriously concerned in polypharmacy among older adults due to altered pharmacokinetics, pharmaco-dynamics as well as physiology related to drug administration such as cognitive function, vision, renal and hepatic function[4]. Furthermore, multiple medication use has been leading to drug-related problems (DRPs), including drug-drug interactions (DDIs), adverse drug events (ADEs), potentially inappropriate medications (PIMs) and non-adherence[5], resulting in increased hospitalization, morbidity and mortality. The definition of polypharmacy has not reached consensus[6,7]; however, polypharmacy has been most frequently defined as simultaneous use of five or more medications[8]. From previous studies, the associated factors with polypharmacy were advanced age, male, the number of health care visits and comorbid diseases and multiple prescribers[6,9-11]. With specific reference to Thailand, no adequate information on related risk factors and DRPs to polypharmacy in the out-patient elderly could be traced. To address this lacuna, this study was aimed at identifying associated risk factors and DRPs with polypharmacy in the context of Thailand.

Material and Methods

Study design and population

The cross-sectional study was conducted in the Internal Medicine Outpatient Clinic, Ramathibodi Hospital, Mahidol University. Recruited participants were 60-year-old adults or older who visited the Internal Medicine Outpatient Clinic, Ramathibodi Hospital, during the period from December 1st, 2015 to May 31st, 2016. In this study, the 452 subjects were categorized into three groups based on the number of concomitant use of medications per day such as the excessive polypharmacy group (>9 medications), the polypharmacy group (5-9 medications) and the no

polypharmacy group (<5 medications) as control group.

Data collection and evaluation

The investigators reviewed medical information during the one year prior to recruitment from the electronic medical records (EMRs) of the 452 subjects, covering demographic characteristics, health care visits, medications, drug administration and DRPs such as ADEs, duplicated medications, DDIs, wrong doses, unnecessary medications and PIMs. Furthermore, the researchers reviewed the results of laboratory investigations.

Baseline characteristics

Participants' data were collected using a structured format, which comprised age, gender, marital status, education, body mass index, insurance, comorbidities, and comorbidity index in Charlson scores[12], lifestyle behaviors, and baseline of basic and instrumental activity of daily livings (BADLs and IADLs)[13,14].

Health care visits

Health care visits' data consisted of the number of doctors who had followed up at outpatient clinics, as well as the frequency of Out-Patient Department (OPD) visits, of Emergency Department (ED) visits and of readmissions within one year before the data were collected.

Medications and drug administration

All drugs, both prescribed and over-the-counter, which were consumed continuously, were reviewed by a geriatrician and clinical pharmacists. Data of medications were recorded by generic name only.

Drug-related problems (DRPs)

The histories of DRPs were reviewed by a geriatrician and clinical pharmacists. DRP is defined as an event involving medication therapy which potentially interfere with desired health outcome. The significant DRPs comprised ADEs, duplicated medications, DDIs, wrong doses, unnecessary medications and PIMs. The definition of ADE is any injuries that occur from medications including drug administration errors and adverse drug reactions (ADRs)[15]. Duplicate medications are defined as two or more of the same medications which are prescribed for the same type of therapy. DDI is a situation in which one substance affects the activity of another drug when both are used simultaneously. In this study, DDIs were

evaluated as minor moderate or major DDIs in all participants by a geriatrician and a pharmacist. Unnecessary medication is described as drug which is prescribed for no obvious indication[16]. The last mentioned DRP was PIM which is defined as the use of medications that should be entirely avoided in the elderly due to risks more than benefits. PIMs were determined by screening tool as Beer criteria 2015[17].

The research protocol was assessed and approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects of the Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Statistical Analysis

All of the statistical analyses for this study were performed with the SPSS for Windows Software Package, Version17 (SPSS Inc., Chicago, Ill., USA). Continuous variables were analyzed by using descriptive statistics: mean±standard deviation or median (range). One way ANOVA or Kruskal-Wallis H test was used to compare baseline characteristics, data of medications and health care visits, data of DRPs and results of investigations among the excessive polypharmacy group, the polypharmacy group and the control group in continuous variables. Categorical data were analyzed as proportions (number, percentage). As for Pearson's chi-square test or Fisher's exact test, categorical variables were used to compare baseline characteristics, data of medications and health care visits, data of DRPs and results of investigations between the three groups. P-values were determined as a significance level with 0.05. The odds ratios indicated the risk factors associated with polypharmacy. The unadjusted odds ratios between the exposure variables and development of polypharmacy were determined by univariate logistic regression analysis. A multivariate ordinal logistic regression analysis and a multivariate multinomial logistic regression analysis were then performed to adjust for these factors that could confound the results and to identify independent risk factors associated with polypharmacy.

Results

Demographic and comorbidity

During the six-month study period at the Internal Medicine Outpatient Clinic, Ramathibodi Hospital, Mahidol University, four hundred and fifty two older adults were enrolled in this study. The mean age of all

participants was 71.01 years (SD=7.83), ranging from 60 to 99 years. This study population comprised two hundred and eighty nine (63.9%) women. In terms of education, the majority of participants (44.6%) had completed primary education. In the case of drug administration, the majority of people administering drugs were the patients themselves (88.7%). In terms of health insurance, more than sixty percent of this population used Civil Servants Medical Benefit Scheme (CSMBS). The participants were classified into three groups, including the excessive polypharmacy, the polypharmacy and the no polypharmacy or control group. From this study, the prevalence of polypharmacy and excessive polypharmacy were approximately 74.8% of the total study population. Baseline characteristics are shown in Table I. The excessive polypharmacy group comprised one hundred and forty three participants (31.1%) and the polypharmacy group consisted of one hundred and ninety five elderly (42.2%), while the no polypharmacy group comprised one hundred and fourteen (24.7%). The percentages of 75-year-old participants or older as well as dependent patients (BADLs' score <12) were significantly different in the excessive polypharamcy and the polypharmacy group, from in the no polypharamcy group (p= 0.002). In terms of comorbidity, the maximum number of chronic diseases was 10 diseases with the mean of number of comorbidities was 3.98 (± 1.54). The number of patients with Charlson comorbidity index of more than three or multiple comorbidities of over three diseases was significantly higher in the excessive polypharmacy and the polypharmacy group than in the control group ($p<0.001$), as shown in Table I. Furthermore, the study revealed that participants in the excessive polypharmacy and the polypharmacy group suffered from specific diseases, including dementia, ischemic stroke, hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), osteoarthritis of knee (OA knee) and chronic obstructive pulmonary disease (COPD) more than the elderly in the control group.

Health care visits

The number of patients with ≥ 3 of OPD and ED visits per year, ≥ 2 of readmission per year and ≥ 3 physicians, which had followed up at outpatient clinics, were significantly greater in the polypharmacy group than the control group ($p<0.001$, $p<0.029$, $p<0.049$ and $p<0.001$ respectively), as shown in Table 1.

Table 1. Demographic and clinical characteristics of the study population

Characteristic	No Polypharmacy Drug <5 items (n=114)	Polypharmacy Drug 5-9 items (n=195)	Excessive Polypharmacy Drug > 9 items (n=143)	p-value
Age, mean (SD), years	68.95(7.17)	71.47(7.83)	72.45(8.07)	
Age 60-75, n (%)	92(80.7)	140(71.8)	90(62.9)	0.007
Age >75, n (%)	22(19.3)	55(28.2)	53(37.1)	
Female, n (%)	75(65.8)	126(64.9)	88(61.5)	0.737
Education >12 years, n (%)	37(35.6)	66(37.3)	48(35.8)	0.946
Self-care, n (%)	107(94.7)	171(88.6)	123(86.0)	0.087
Civil Servants Medical Benefit Scheme, n (%)	61(53.5)	129(66.2)	94(65.7)	0.085
Charlson comorbidity index >3, n (%)	50(43.9)	119(61.0)	99(69.2)	<0.001
Comorbidities				
Number of Comorbidities >3, n (%)	45(39.5)	129(66.2)	109(76.2)	<0.001
Dementia, n (%)	0(0)	2(1.0)	7(4.9)	0.011
Ischemic stroke, n (%)	10(8.8)	42(21.5)	27(18.9)	0.015
Hypertension, n (%)	86(75.4)	172(88.2)	115(80.4)	0.012
DM, n (%)	19(16.7)	89(45.6)	69(48.3)	<0.001
CKD, n (%)	13(11.4)	33(16.9)	36(25.2)	0.015
OA knee, n (%)	8(7.0)	25(12.8)	33(23.1)	0.001
COPD, n (%)	1(0.9)	2(1.0)	7(4.9)	0.033
Smoking, n (%)	9(8.5)	10(5.8)	11(8.5)	0.599
Drinking, n (%)	8(7.5)	9(5.3)	7(5.5)	0.711
BADLs score≤ 12, n (%)	2(1.8)	9(4.8)	17(12.1)	0.002
IADLs score <5, n (%)	1(0.9)	9(5.1)	7(5.5)	0.142
Healthcare services				
OPD visits ≥ 3, n(%)	87(76.3)	159(81.5)	140(97.9)	<0.001
ED visits ≥ 3, n(%)	1(0.9)	4(2.1)	9(4.6)	0.029
Readmission ≥ 2, n(%)	2(1.8)	1(0.5)	6(4.2)	0.049
Number of physicians ≥ 3, n(%)	68(60.7)	127(65.1)	124(87.9)	<0.001
Laboratory investigation				
Hct ≥ 36%, n(%)	22(23.9)	43(27.9)	52(43.7)	0.003
BUN >20 (g/dl), n (%)	5(5.4)	34(19.7)	30(24.8)	0.001
Alb ≤ 30 (mg/dl), n (%)	6(9.0)	4(3.5)	14(14.4)	0.018

Abbreviations: DM, Diabetes mellitus; CKD, Chronic kidney disease; OA knee, osteoarthritis of knee; COPD, chronic obstructive pulmonary disease, BADLs; basic activity of daily livings; IADLs, instrumental activity od daily livings, OPD, out-patient department; ER, emergency department; Hct, hematocrit; BUN, blood urea nitrogen; Alb, albumin

DRPs associated with polypharmacy

This study presented the prevalence of DRPs associated with polypharmacy such as ADEs (2.7%), PIMs (62.9%), duplicated drugs (2.1%), unnecessary drugs (72.4%), DDIs (91.4%) and wrong dose (0.2%), as shown in Table 2. Most DDIs were minor and moderate interactions (70% of total DDIs). There was no ADE, resulting from DDIs. Vitamin was the most common used medications as unnecessary medication. Three most common of used medications in the present study were statin, vitamin and calcium channel blocker, as shown in Figure 1.

Table 2. Drug-related problems associated with polypharmacy

Category of drug-related problems	**No Polypharmacy Drug <5 items (n=114)**	**Polypharmacy Drug ≥ 5 (n=338)**	**p-value**
Adverse drug events (ADEs)	3(2.6)	9(2.7)	1.000
Potentially inappropriate medications (PIMs)	14(12.5)	212(62.9)	<0.001
Duplicated drugs	-	7(2.1)	0.200
Unnecessary Medications	13(11.6)	244(72.4)	<0.001
Drug-drug interactions (DDIs)	38(33.9)	308(91.4)	<0.001
Wrong dose	-	1(0.2)	1.000

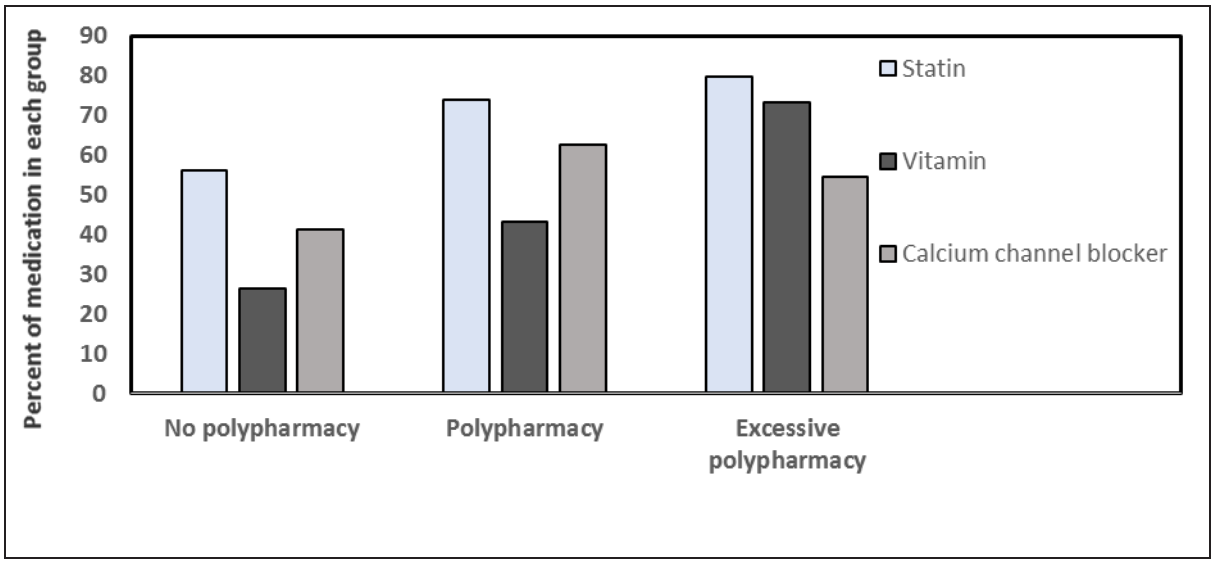

Figure 1. Common used medications of the study population

Factors associated with polypharmacy

The results of the multivariate ordinal logistic regression analysis for relevance to a higher polypharmacy were presented in Table 3. Four or more chronic diseases especially in dementia, DM and OA knee, three or more physicians or OPD visits and dependent status were relevant to polypharmacy and excessive polypharmacy. Results from the multivariate multinomial logistic regression analysis of relevant risk factors to each category of polypharmacy were shown in Table 4. The key results of this analysis were summarized in Figure 2. Compared to a no polypharamcy group (reference: OR=1.0), dependent status, four or more of chronic diseases especially in DM and OA knee, and three or more of OPD visits or of physicians were each independently correlated with excessive polypharmacy exposure, whereas either DM or four or more of chronic diseases was significantly related to exposure of polypharmacy and of excessive polypharmacy.

Table 3. Multivariate Ordinal Logistic Regression Analysis of risk factors relevant to a higher polypharmacy

Variables	OR (95% CI)	p-value
Dementia	12.68 (1.36-117.33)	0.026
DM	2.05 (1.39-3.08)	0.001
OA knee	2.36 (1.36-4.06)	0.002
OPD visits ≥ 3	2.34 (1.28-4.28)	0.006
Number of physicians ≥ 3	1.73 (1.09-2.75)	0.019
Number of Comorbidities >3	1.82 (1.20-2.76)	0.005
BADLs score ≤ 12	3.53 (1.53-8.07)	0.003

Abbreviations: DM, Diabetes mellitus; OA knee, osteoarthritis of knee; OPD, out-patient department; BADLs; basic activity of daily livings

Table 4. Multivariate Multinomial Logistic Regression Analysis of risk factors relevant to each category of polypharmacy (No polypharmacy; drugs 0-4 items = reference)

Variables	Drugs 5-9 items (n=195; 43.1%)		Drugs > 9 items (n=143; 31.6%)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Diabetes mellitus	3.47 (1.89-6.37)	<0.001	3.61 (1.86-7.02)	<0.001
OA knee	1.45 (0.59-3.50)	0.412	2.97 (1.22-7.21)	0.016
OPD visits ≥ 3	1.40 (0.69-2.85)	0.349	11.14 (2.36-52.66)	0.002
Number of physicians ≥ 3	0.97 (0.53-1.77)	0.932	2.51 (1.19-5.30)	0.016
Number of Comorbidities >3	1.79 (1.05-3.07)	0.033	2.28 (1.23-4.25)	0.009
BADLs score ≤ 12	3.44 (0.70-16.86)	0.128	9.60 (1.92-48.11)	0.006

Abbreviations: DM, Diabetes mellitus; OA knee, osteoarthritis of knee; OPD, out-patient department; BADLs; basic activity of daily livings

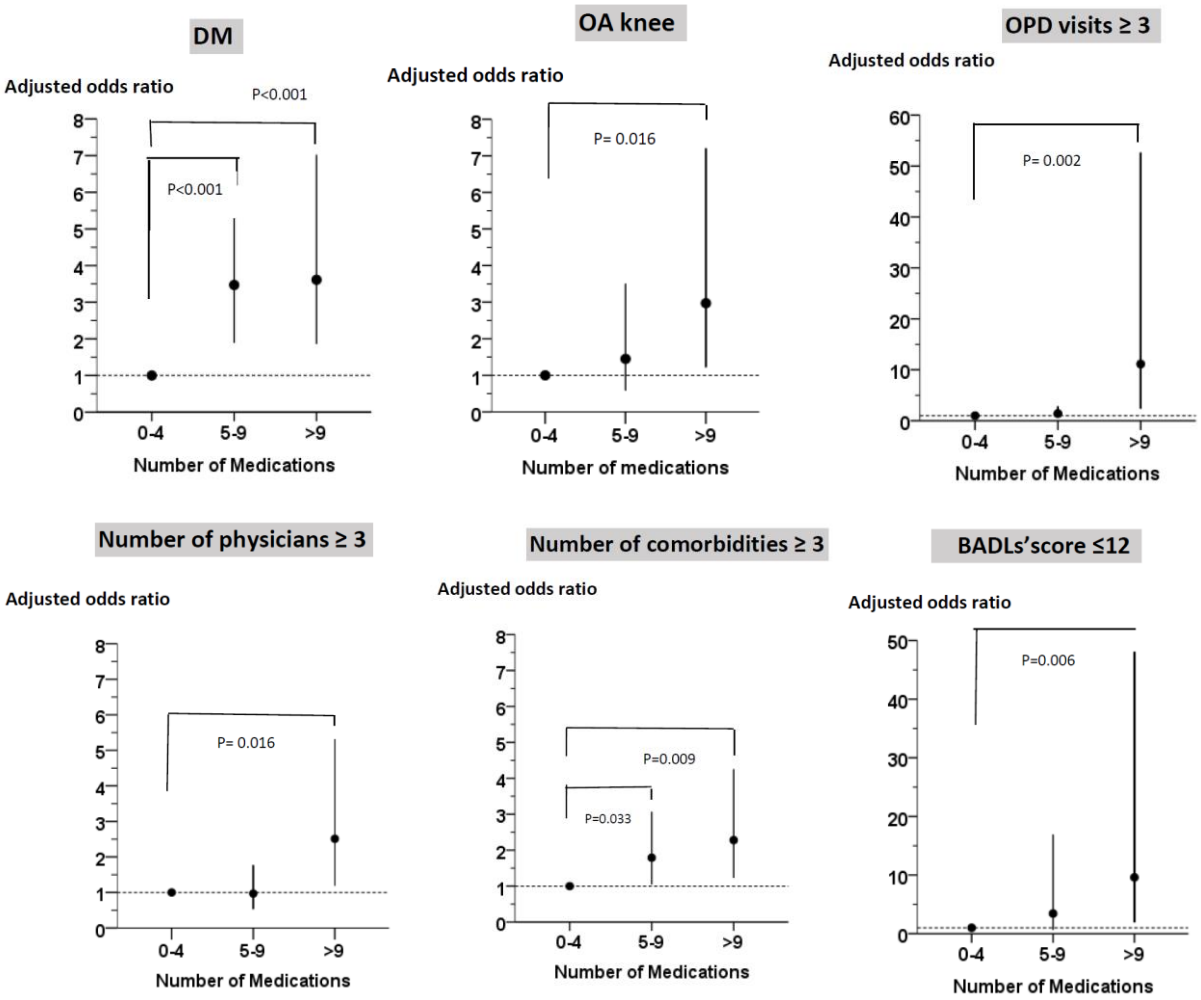

Figure 2. Representative graphs of the results of a multinomial logistic regression analysis. The graphs show odds ratios (dots), 95% confidence intervals (bars), and P values. (DM, Diabetes mellitus; OA knee, osteoarthritis of knee; OPD, out-patient department; BADLs; basic activity of daily livings**)**

Discussion

The present study showed the risk factors of polypharmacy and of excessive polypharmacy and the DRPs associated with polypharamcy in outpatient clinics of the tertiary care setting in Thailand. From this study, the results revealed that the prevalence of polypharmacy was more than 70% of the total study population, which was one of the common problems in outpatient clinics, while previous studies in Thailand, there are only studies in the primary care which the prevalence of polypharmacy was 29-36.8%[2,3]. The result of polypharmacy's prevalence reflected that most polypharmacy have occurred in tertiary care setting instead of primary care setting. The risk factors of an increased rate of excessive polypharmacy were dependent status (BADLs' score < 12), four or more of chronic diseases especially in DM and OA knee, and increased OPD visits or physicians, while in another study[18], increasing functional impairment decreased the rate of excessive polypharmacy. In terms of comorbidities, in this study, DM was strong risk factor associated with polypharmacy ($p<0.001$), correlating with one previous study[19] which explained by being of the high probability of co-chronic diseases with simultaneous medication use. Bjerrum et al[20], presented that in the elderly exposed to polypharmacy, analgesics including nonsteroidal anti-inflammatory drugs or NSAIDs were frequently used medications which were usually consumed in patients with OA knee in the present study. Increased frequency of health care visits was certain another one significant risk factor of polypharmacy in several previous studies[6,11] including this study. In terms of used medications, three most frequently used medications were statin, vitamin and calcium channel blockers as well as another previous study[8] presented that antihyperlipidemia was one of most common frequently used medications associated with polypharmacy. The use of multiple medications was associated with the elevation of DDIs ADEs, PIMs, unnecessary medications and duplicated medications[21-23]. The severe DDIs were approximately 30 %; however, there was no ADEs from these DDIs. PIMs in this study were evaluated by criteria of consumption of avoiding medications due to risks more than benefits, but were not assessed by combination of previous criteria with prescribing cascade[23,24]. Therefore, the prevalence of PIMs in the study may be

underestimated. According to Beers criteria 2015, the common medications related to PIMs were anticholinergic drugs, benzodiazepines and NSAIDs[8,25]. The prevalence of unnecessary medications in this study (72.4%) is higher than previous study[23]. Proton pump inhibitors were usually used to prophylactic therapy for patients with low dose aspirin who was no history of peptic ulcer or indication[23]. Another common unnecessary medication was vitamin which was the first most common frequently used medication in the present study. From the results, the researchers have to be aware of problems of physicians' drug prescription and administration which may result in polypharmacy and associated DRPs. Therefore, latter future project will develop new systems to monitor PIMs and DDIs in electronic dispensing systems and create education programme for physicians and pharmacists to prevent polypharmacy and DRPs in the elderly population.

The strengths and limitations of this study

The present study had several advantages to be presented. Firstly, the researcher reviewed prescribed drugs over one year before gathering data; therefore, most medications were completely reviewed in this study such as daily, weekly and monthly medications and short period of drug use. Secondly, polypharmacy in this study included both topical drugs such as eye drops and dermatological drugs and systemic medications which may develop DRPs. Finally, the data were reviewed by well-trained geriatricians and clinical pharmacists; therefore, most data were clarified and valid.

In this study; however, there were some disadvantages. Firstly, this study was limited to only one tertiary hospital and to only Thai population so that the results may not be applied to other facilities or to other nationalities. Secondly, some of the collected data were incomplete due to missing data in EMRs. Thirdly, the detection of PIMs should apply criteria prescribing cascade and should certainly evaluate reason of drug administration with Beer criteria 2015 to address underestimation of PIMs. Finally, according to retrospective cohort study, researchers may not accurately assess reason and time sequence of drug administration.

Conclusion

The polypharmacy is one of the most common of problems in the elderly aged 60 or over. More than 60% of older adult with

polypharmacy have PIMs, unnecessary medications and DDIs. To address polypharmacy, the efficient monitoring DRPs and examination of physicians' prescriptions and patients' drug use should be done. Moreover, the early recognition for related factors should also be initiated to decrease the polypharmacy. Besides awareness of polypharmacy, evaluation of reason and time sequence of drug administration is essential, resulting in accurate assessment of appropriate drug use.

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Conflict of interest

The authors declare that no conflicts of interest.

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