Associations between drug burden index, medication appropriateness and patient-reported outcomes in the community pharmacy setting in Malaysia

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ABSTRACT

Introduction The increasing complexity of drug regimens over time and the use of multiple medications exposes older patients to a greater risk of receiving inappropriate medications. The study aims to investigate whether drug burden index (DBI) and potentially inappropriate medications (PIMs) were associated with patient-reported health outcomes (PROs) in community-dwelling older adults (aged ≥60 years) in Malaysia.

Methods DBI used to quantify patients' exposure to anticholinergic and sedative medications in a cross-sectional sample of older individuals from the community pharmacy setting in Malaysia. PIMs (based on Beers criteria), potentially inappropriate prescribing (PIP; based on STOPP criteria) and polypharmacy (use of ≥ 5 concurrent medications) used to quantify exposure to in appropriate medications. PROs were investigated using the Groningen Frailty Indicator (GFI) for frailty, and Older People's Quality of Life-35 (OPQOL) for quality of life (QOL). The adjusted associations between DBI, medication inappropriateness and PROs were analyzed.

Results More than half of the study participants received ≥ 1 anticholinergic or sedative medication (mean 0.47/participant; range 0.0–2.14). Prevalence of frailty was low; 8.90% of patients with a mean GFI score of 1.67 (range 1–8) and was significantly and positively correlated with DBI (r 0.253; p = 0.003). In multivariate logistic regression, frailty was found to be significantly associated with the odds of receiving DBI-associated medications (odds ratio 1.44; 95% CI 1.02–2.02, p = 0.039). Non-significant associations between DBI and QOL domains, except significant and positive correlation between independence domain of OPQOL and PIPs.

Conclusion The study indicates a significant relationship between drug burden measured by DBI, and frailty measured by GFI. The prescribers managing various medical conditions of older people should consider frailty and other relevant physical health parameters as important health outcomes.

Introduction

The ageing population is poised to become one of the most significant social transformations of the 21st century [1]. The World Health Organization predicts an estimated growth of global aging population from 524 million in 2010 to 105 billion in 2050 [2]. Similarly, in Malaysia, as of 2015, 8.0% of the total population consisted of people aged > 60 years [3]. With the decline in fertility and mortality rates, however, the proportion of older people will expand by 2030 and is predicted to account for 15.0% of the total population [1,2].

Aging is significantly associated with the development of comorbid chronic conditions, which warrants the use of multiple medications, as per clinical guidelines [3]. Aging is commonly characterized by the emergence of several complex health states, commonly called geriatric syndromes, which highlights unique and common features of health conditions in older people [4]. This includes frailty, urinary incontinence, falls, delirium and pressure ulcers [5-8]. Frailty leads to a state of vulnerability and impaired ability to adapt to external stressors [6], and increases the risk of dependency and adverse events (e.g. cognitive and functional status decline, disabilities, institutionalization and hospitalization) [6]. Frailty coupled with multiple impairments complicate treatment and limit drug choices among older people.

Complexity of drug regimen among older people continues to increase over time, as multiple medications are required to treat a single condition. As a result, polypharmacy is prevalent among older people, with reports of over 45.9% urban community-dwelling older adults in Malaysia receiving ≥5 medications [9]. Polypharmacy is commonly associated with suboptimal prescribing, which is significantly linked to deterioration in physical functioning status [10,11]. Internationally, Gnjidic et al.investigated the association between the Drug Burden Index (DBI), a tool measuring an individual's exposure to sedative and anticholinergic drugs, and the Beers Criteria, a measure of potentially inappropriate drug use, with function in older adults residing in self-care retirement villages [12]. Kojima et al. reviewed the association between frailty and quality of life (QOL) among community-dwelling older people [13]. The literature also vastly

discusses the improvement in quality of medicines use and patient-reported health outcomes (PROs) via medication reviews for older people [14], with Castelino et al. supporting such improvements when home medicines review services for community-dwelling older people were performed by pharmacists [15]. However, these studies do not focus on the assessment of medication appropriateness and drug burden to optimize functional performance and abilities in frail individuals and those with poor QOL. In addition, there are limited studies investigating such associations among community-dwelling older people in Malaysia (5,11). Hence, the aim of this study is to examine whether DBI and inappropriate medicines use were associated with PROs in community-dwelling older adults in Malaysia.

Methods

Study design, participants and setting

This was a cross-sectional study conducted among community-dwelling older people who visited community pharmacies between July and September 2017. This study assessed associations between DBI (i.e. exposure to anticholinergic and sedative medicines), medication inappropriateness and PROs in the community pharmacy setting. Community pharmacies from areas representing different geographic locations were selected because of their convenient accessibility and proximity to the researcher. In total, four community pharmacies, operated by private owners, in Kuala Lumpur and Selangor (both of which are in in peninsular Malaysia) participated in the study.

Participants were included if they had been visiting a community pharmacy, were aged ≥60 years, were mobile, had ≥ 1 long-term medical condition, had received ≥ 1 long-term medication, were articulate in English and provided informed consent to participate. An interviewer-administered comprehensive assessment form (CAF) was used to collect demographic data (age, sex, race, marital status, education level, occupation history, number of children and siblings, physical activity level, smoking and alcohol status), QOL, mental health status, frailty status, and medication and medical history, from participants.

Our investigation complies with the standards of the Helsinki declaration concerning investigation with human subjects. The International Medical University Joint-Committee on Research and Ethics (Project ID: BPI-1-14-(09)2017) provided ethical approval for the study. Permissions from individual community pharmacies were also obtained before data collection. Participants' personal data were stored in a password-protected file accessible only to the researchers. No personal data was disclosed, and the study results are reported as de-identified data.

Assessment of medication inappropriateness

The inappropriateness of medications was assessed using the Beers criteria (2015), which identifies potentially inappropriate medications (PIMs), and the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria (2014), which identifies potentially inappropriate prescribing (PIP) [16,17]. Both are based on a medicine-to-avoid list by expert consensus [16,17].

The use of medicines use was primarily based on patients' medical records obtained from each participating community pharmacy. The data collected included the name, dose, and dose instructions for all medications used in the 3 months prior to the start date of the study at each facility. Exposure to a PIM, PIP or DBI medication was defined as exposure to an affected medication during the 3-month period.

Assessment of drug burden index

The DBI was used to quantify individuals' total exposure to anticholinergic and sedative medication, using the following formula [18-20]:

$$DBI = \frac{D}{D + \delta}$$

where *D* is the daily dose taken by the individual within 24 h (derived from dosing instructions available through medical records), and δ is the minimum efficacious dose which was approved and registered by the Ministry of Health Malaysia (Formulari Ubat KKM (FUKKM, March 2016). The Malaysian product information and Monthly Index of Medical Specialties (MIMS Malaysia; 2017) were used to identify medications with

clinically significant anticholinergic and/or sedative effects. Complementary medications, health supplements and medications prescribed on a when required basis were excluded from the DBI calculations (see Supplementary Table for DBI calculation).

Patient-reported health outcomes

The PROs evaluated were the Groningen Frailty Indicator (GFI), Older People's Quality of Life (OPQOL) inventory, and the Hospital Anxiety and Depression Scale (HADS). The GFI consists of 15 dichotomous items, ranging from a total score of 0 (normal activity without restrictions) to 15 (completely disabled); participants with scores ≥ 4 were considered frail [21]. We have validated the GFI tool and reported our findings elsewhere [22]. OPQOL was used to assess QOL in 9 domains: overall life, health, social relationships, independence, control over life, freedom, home, and neighborhood, psychological and emotional wellbeing, finance, and religion/ culture [23]. Total OPQOL scores range from 35 (worst possible QOL) to 175 (best possible QOL) [23]. In this study, polypharmacy was defined as ≥ 5 concurrent medications being dispensed at any one time during the study period, with participants' medication details being obtained from the interview [24]. HADS was used to screen emotional disorders of participants in non-psychiatric settings by detecting anxious and depressive states, which are the two most frequent distress expressions [25]. It consists of a list of questions, with scores ≥11 for either domain indicating the anxious and depressive states [25].

Sample size and sampling

The estimated study sample size was 135, based on the percentage prevalence of Malaysian population aged ≥ 60 years, with a 95% confidence level and 4% margin of error [26]. About 170 older people from community pharmacies in the Kuala Lumpur and Klang Valley regions were approached. Of these, 135 participants who met the inclusion criteria and provided informed consent were included. Before each interview, consent (either verbal or written) was obtained after explaining research objectives to the participants who corresponded to the inclusion criteria. Each interview was conducted in the English language using interviewer-administered CAF. Participants were identified with the help of pharmacist working at the sampled pharmacies.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS version 24) ® with a significance level of 0.05. The collected data are presented as frequencies, percentages, means and standard deviations. Chi-square test was used to compare PROs and medication-related variables (e.g. frailty and polypharmacy; frailty and DBI). Spearman correlation was used to determine the underlying relationship between variables such as DBI, medication appropriateness and PROs. GFI, OPQOL, and HADS scores were changed to binary variables. The median split method was used to split total OPQOL scores (35 to 175) into binary variables (good and poor QOL) [27]. A HADS score of 7 was used to categorize cases and non-cases of depression and anxiety. Unadjusted and adjusted binary logistic regression models were used to examine associations between (1) exposure to a PIM according to the Beers Criteria (yes or no), (2) exposure to a PIP (yes or no) or (3) having a DBI>0 and GFI, OPQOL, and HADS measures (binary variables). The potential confounders were identified based on their association with main variables and based on a priori knowledge [16-20]. We determined variables necessary to control for a confounding effect and that includes age, sex, marital status, number of medications, PROs, and medication-related variables.

Results

Socio-demographic characteristics of participants

A total of 135 community-dwelling older adults participated in this study. Female and Chinese participants constituted ≈46% and 64% of the total sampled population, respectively. The mean age of participants was 68.89 ± 6.14 years, with the majority of them (94 patients; 69.60%) being aged 60–69 years. Almost all participants (131; 97.00%) were married (**Table 1**).

Patient-reported health outcomes (PROs)

About 9% of the participants fell into the frail category (defined as a GFI score of ≥4), with a mean score of 1.67 ± 1.387 (range 1-8). The mean total OPQOL score was 130.30

± 8.01 (range 109-157) with leisure and activities as the highest domain scored in OPQOL (**Table 2**).

Use of medicines by the participants

The mean number of medications per participant was 2.34 ± 1.37 (range 1-7). Polypharmacy (≥5 medications) was received by ≈8% (n = 11) of participants, and ≥ 1 PIM or PIP by 8.90% (n=12) and 5.20% (n=7) of patients, respectively. About 59% (n=80) of the participants received ≥ 1 anticholinergic and/or sedative medication included in the DBI (mean 0.47/patient; range: 0–2.14; **Table 3**).

Drug Burden Index, inappropriate medications and PROs

Exposure to inappropriate medications (including PIMs, PIPs and polypharmacy) occurred in < 10% of the frail population in the community pharmacy setting. The difference in mean PIMs was statistically significant between frail and non-frail participants (0.13 vs 0.03, p=0.001). However, the differences in average PIPs and DBI between frail and non-frail participants were not significant. There was a significant and positive correlation of GFI with number of PIMs (*r* 0.255; *p*=0.003) and DBI (*r* 0.253; *p*=0.003) in the correlation analysis.

In the total study population, being exposed to ≥1 PIM or PIP according to the Beers and STOPP Criteria was not significantly associated with the total OPQOL score when compared to not being exposed to a PIM or PIP. Among all OPQOL domains, the only significant and positive correlation was between the independence domain of OPQOL and number of PIPs (*r* 0.172; *p*=0.046). The correlation analysis also found a significant and positive relationship between DBI and polypharmacy (*r* 0.319; *p*=0.001).

In the multivariate logistic regression, frailty was found to be significantly associated with the odds of receiving DBI-associated medications (odds ratio1.44; 95% CI: 1.02 – 2.02, p=0.039), as depicted in **Table 4**. Frailty was also significantly associated with exposure to a PIM in the unadjusted model, but became insignificant after adjustment for potential confounders. The OPQOL scores were associated with an increased risk of receiving DBI-associated medications, PIM and PIP, but their associations were not statistically significant.

Discussion

The present study examines drug burden and its relationship with medication inappropriateness and PROs in community-dwelling older people in Malaysia. In this community-based study, frail older people were exposed to greater anticholinergic and sedative load than non-frail participants. As a result, frail participants have greater reported medication burden quantified by DBI compared with non-frail participants. Furthermore, the association remained significant even after adjustment for covariates. The findings from this study were consistent with studies conducted in different countries (USA, Australia and Finland), despite the differences in healthcare access and medication exposure [28-30]. According to some literature, the presence of frailty contributes to the development and progression of multiple chronic comorbidities [31]. As a result, older frail people experience greater complexity in medication regimen, which commonly involves anticholinergic and sedative medications.

Rational prescribing among older people is complex due to lack of medication effectiveness and safety data in this age group [32,33], resulting in a high prevalence of inappropriate medication use among older people. More than half of the older people in this study were exposed to DBI-associated medications and there seemed to be a significant and positive correlation between GFI and medication inappropriateness. The findings from this study are consistent with a retrospective analysis conducted by Castelino et al. in older community-dwelling older individuals prior to a medication review intervention, in which the majority of participants were exposed to DBI-associated medications and one-third had PIMs [15]. This can be explained by age-related changes in pharmacokinetics and pharmacodynamics among older people [34]. Furthermore, the frail elderly people are also known to be more intolerant of medications than their fit counterparts [34, 35]. They have a diminished ability to adapt to changes with impaired homeostatic mechanisms and decrement in their hepatic metabolism. Indeed, they are expected to portray an exaggerated response to medications [35].

Poorer QOL was also associated with medication inappropriateness. Although there was no statistically significant association identified between both parameters, there was a statistically significant association between medication inappropriateness and the

physical health domain measured by OPQOL-36. Harrison et al. depicted similar findings in a cross-sectional study with a significant association between higher DBI and poorer QOL, as well as increasing PIMs and poorer QOL [36]. This can be explained by the nature of inappropriate medication use, which commonly leads to adverse outcomes that affects participants' morbidity and QOL [37, 38]. In contrast, there was a statistically significant and negative association between medication inappropriateness and dependency. This, however, contradicts several studies that have reported a positive correlation between both parameters. This could be due to the setting of this study as the participants were non-institutionalized individuals with better health status [38, 39] than those in settings such as aged-care facilities, nursing homes and retirements villages [36, 37].

Many studies have investigated medication use and high-risk prescribing among community-dwelling older people [16,24,30,32,33]. However, to the authors' knowledge, this was the first study in Malaysia (or the region) that investigated the association between medication burden and medication appropriateness. The study has shown statistically significant correlation between medication burden and medication inappropriateness. More participants with DBI > 0 than those who were not exposed to DBI-associated medications (DBI = 0) had inappropriate medication use, as shown by the proportions of patients exposed to a PIM (58.33 vs 41.67%). PIP (57.14 vs 42.86%) or polypharmacy (90.91 vs 9.09%). Anticholinergics and sedatives were common inappropriate medications prescribed among older people.

There are several strengths to the study. Both implicit and explicit tools were used to measure medication appropriateness. Validated tools were used in this study to investigate medication appropriateness, drug burden and physical health outcomes. However, some limitations could affect the generalizability of the study findings. Firstly, the cross-sectional study design is not suitable to determine the nature of the temporal relationship between medication appropriateness, drug burden and physical function parameters as the exposure and outcome are assessed simultaneously. Secondly, low reliability in self-reported medication use, history and medical conditions may result in an underestimation of medication appropriateness and drug burden. Thirdly, DBI

calculations use the minimum recommended daily dose, which may vary depending on medication-related pharmacokinetic and pharmacodynamic differences, as well as inter-individual variability. This could have caused biasness when determining the pharmacodynamic contribution of individual medications [19]. Fourthly, the use non-probability sampling (convenience sample) may result in selection bias. Lastly, the unadjusted and adjusted effect sizes are generally biased in most studies except randomized studies. In general, as the sample size increases, the risk of getting biased r-squared would get smaller. We preferred logistic regression because an equivalent statistic to R-squared does not exist (depends on pseudo R-squared values).

In conclusion, the present study found a significant relationship between high-risk prescribing (e.g. higher DBI-associated medications) and PROs such as frailty and QOL. However, exposures to both DBI and medication inappropriateness were not significantly associated with overall QOL. Medication inappropriateness measured by PIM, PIP and polypharmacy was higher among DBI-exposed participants. The prescribing of medications for managing various medical conditions among older people should consider frailty or other physical health parameters as part of a disease prognosis. Further longitudinal studies investigating the impact of drug burden due to suboptimal prescribing and its association with functional deterioration is important to study the nature of the association.

Compliance with Ethical Standards

Funding: None.

Conflict of interest: All authors declare that they have no conflicts of interest.

Acknowledgments

We thank the International Medical University and the management of community pharmacies for the support during this study and extend our appreciation to all participants who took part in the study.

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1 Socio-demographic parameters of participants (*n*=135)

Variables	No. of pts (%)
Age[a]	
60 – 69 years	94 (69.60)
70 – 79 years	34 (25.20)
≥80 years	7 (5.20)
Sex	
Female	62 (45.90)
Male	73 (54.10)
Race	
Chinese	87 (64.40)
Malay	23 (17.00)
Indian	24 (17.80)
Marital status	
Married	131 (97.00)
Single	4 (3.00)
[a]Mean age 68.89 years ± 6.14 (SD)	
Pts participants, *SD* standard deviation	

Table 2: Patient-reported health outcomes of participants (*n*=135)

Variable	Value	Minimum	Maximum
Groningen Frailty Index scores (possible range: 0–15)			
Mean score ± SD	1.67 ±1.39	1	8
No. of non-frail pts (score <4) (%)	123 (91.10)		
No of frail pts (score ≥ 4) (%)	12 (8.90)		
Hospital Anxiety and Depression Scale scores (possible range: 0 – 42)			
Mean total score ± SD	5.49 ± 6.83	0	35
Mean anxiety score (SD)	3.90 ± 4.54	0	21
Mean depression score ± SD	1.59 ± 2.67	0	14
No. of pts without anxiety (score 0-7) (%)	108 (80.00)		
No. of pts with anxiety (score 8-21) (%)	27 (20.00)		
No. of participants without depression (score 0-7) (%)	130 (96.30)		
No of pts with depression (score 8-21) (%)	5 (3.70)		
OPQOL scores (possible range: 35–175)			
Mean total score ± SD	130.30 ± 8.01	109	157
No. of pts with good OPQOL (%)	61 (45.20)		
No. of pts with poor OPQOL (%)	74 (54.80)		
OPQOL domain scores ± SD			
Life overall (possible range: 4 – 20)	15.52 ± 2.36	8	20
Health (possible range: 4 – 20)	15.34 ± 2.01	10	20
Social relationships (possible range: 5 – 25)	15.94 ± 0.62	14	18
Independence, control over like, freedom (possible range: 4 – 20)	16.09 ± 1.27	11	20
Home and neighborhood (possible range: 4 – 20)	15.90 ± 1.55	12	20
Psychological and emotional well-being (possible range: 4 – 20)	14.22 ± 1.28	11	20
Financial circumstances (possible range: 4 – 20)	16.04 ± 2.40	8	20
Leisure and activities (possible range: 6 – 30)	21.25 ± 1.94	15	25

OPQOL Older Peoples' Quality of Life version 36, *pts* participants, *SD* standard deviation

Table 3 Medicines use, drug burden and medication inappropriateness (*n*=135)

Variables	Value
Mean no of medications per pt ± SD (range)	2.34 ± 1.37 (1–7)
No. of pts receiving polypharmacy (%)	11 (8.10)
No. of pts exposed to a PIM (%)	12 (8.90)
Mean no. of PIMs per pt ± SD (range)	0.36± 0.13 (0–1)
No. of pts exposed to a PIP (%)	7 (5.20)
Mean no. of PIPs per pt ± SD (range)	0.02 ± 0.11(0–1)
No. of pts with DBI > 0 (%)	80 (59.30)
Mean DBI score ± SD (range)	0.47 ± 0.49 (0–2.14)

DBI Drug Burden Index, *PIM* potentially inappropriate medication, *PIP* potentially inappropriate prescribing, *pt(s)* participant(s), *SD* standard deviation

Table 4 Unadjusted and adjusted odds ratios (95% CI) of reporting exposure to DBI, PIMs, and PIPs, by patients' health outcomes (*n*=135)

Variables	Odds ratio (95% CI), p-value[a]			
	Polypharmacy	DBI score > 0	Exposure to a PIM	Exposure to PIP
Unadjusted models				
Frailty (GFI score)	1.26 (0.87-1.82), 0.213	**1.34 (1.01 – 1.80), 0.048**	**1.77 (1.24 – 2.58), 0.002**	1.10 (0.66 – 1.81), 0.719
OPQOL score	1.00 (0.96-1.08), 0.571	0.99 (0.95-1.03), 0.588	0.95 (0.88 – 1.03), 0.203	1.04 (0.94 – 1.14), 0.467
Adjusted models[b]				
Frailty (GFI score)	1.18 (0.76 – 1.83), 0.452	**1.44 (1.02 – 2.02), 0.039**	1.56 (0.96 – 2.54), 0.075	2.02 (0.77 – 5.30), 0.152
OPQOL score	1.01 (0.92 – 1.10), 0.924	1.00 (0.94 – 1.05), 0.936	1.01 (0.92 – 1.10), 0.842	1.02 (0.92 – 1.14), 0.688

Referents were no polypharmacy, DBI = 0, no exposure to a PIM or PIP

DBI Drug Burden Index, *GFI* Groningen Frailty Index (range 0–15); *OPQOL* Older Peoples' Quality of Life version 36 (range 35–175), *PIM* potentially inappropriate medication, *PIP* potentially inappropriate prescribing

[a]Bolded values indicate statistically significant between-variable differences

[b]Odds ratio adjusted for age, sex, marital status, no of medications, Hospital Anxiety and Depression Scale scores, OPQOL, GFI, polypharmacy, PIM, PIP, DBI. Classification method used was logistic