Journal of Pharmacy

ORIGINAL ARTICLE

Open Access

Prevalence, Factors and Cost Comparison due to Potentially Inappropriate Medications (PIMs) of Elderly Outpatients in a State Hospital in Malaysia.

Wei Chern Ang[1,2*], Nur Syafiqah Zulkepli[2], Nur Safinaz Mukhtar[2,3] and Nur Atikah Zulkefli[2]

ABSTRACT

Introduction: Malaysia will be a full aging nation by 2030. The elderly (aged ≥65 years old) population often has multiple comorbidities, which increases the risk of polypharmacy and potentially inappropriate medications (PIMs). This study aims to investigate the prevalence, factors associated with PIMs among elderly outpatients, and its burden of direct pharmacotherapy cost to the Ministry of Health Malaysia.

Materials and method: A cross-sectional study involving clinic prescriptions among the elderly with more than one-month prescribing duration received from a tertiary hospital specialist clinic pharmacy from March to April 2017. Patient identifiers were screened using the Pharmacy Information System (PhIS) by including prescriptions from other clinics while excluding multiple visits and duplicate prescriptions. Patients were categorised as PIM group and non-PIM groups using Beers Criteria 2015. Logistic regression analysis was conducted to examine the factors associated with PIMs. The median monthly prescription cost was compared between PIM and non-PIM groups by Mann-Whitney test.

Results: Among 472 patients, 39.4% of patients had at least one PIM while 60.6% of patients did not receive any PIM. The number of medications prescribed was an independent risk factor contributing to PIMs (OR:2.04; 95% CI:1.40, 2.97). The median monthly prescription cost for the PIM group was MYR 29.50 (≈USD 7.53) which was not statistically significant (p=0.735) compared with the non-PIM group which was MYR 28.50 (≈USD 7.28).

Conclusion: PIM was frequently prescribed in our setting with the number of medications as the only factor. However, the prescribing of PIM did not add nor reduce the direct cost of pharmacotherapy.

ARTICLE HISTORY:

Received: 1 September 2020
Accepted: 1 December 2020
Published: 8 January 2021

KEYWORDS:

Potentially inappropriate medication, cost, elderly, outpatient, patient safety.

HOW TO CITE THIS ARTICLE:

Ang, W. C., Zulkepli, N. S., Mukhtar, N. S. & Zulkefli, N. A. (2021). Prevalence, Factors and Cost Comparison due to Potentially Inappropriate Medications (PIMs) of Elderly Outpatients in a State Hospital in Malaysia. *Journal of Pharmacy,* 1(1), 27-33.

***Corresponding author:**

Email address: wei.ang.1990@gmail.com
Tel:+604 9738413

Authors' Affiliation:

[1] *Clinical Research Centre, Hospital Tuanku Fauziah, Ministry of Health Malaysia, Jalan Tun Abdul Razak, 01000 Kangar, Perlis, Malaysia*
[2] *Department of Pharmacy, Hospital Tuanku Fauziah, Ministry of Health Malaysia, Jalan Tun Abdul Razak, 01000 Kangar, Perlis, Malaysia*
[3] *University Health Centre, Universiti Utara Malaysia, 06010 Sintok, Kedah, Malaysia*

JOP

Introduction

Population ageing is a phenomenon in which people live a longer life and takes place nearly in almost all countries in the world. The reduction in mortality led to an increase in population survival rate, thus increasing the proportion of elderly. The United Nations takes 60 years old and above as age reference for geriatrics. However, in most developing countries, the age of 65 is used as a cut-off as this is the age at which citizens are eligible for elderly social security payments (Guzmán, Pawliczko, & Beales, 2012). In Malaysia, the proportion of elderly aged 65 years and over had increased to 5.1% according to the National Population and Housing Census 2010, as compared to 3.9% in 2000, with a projection of increment of 0.1% per year (Hairi, Bulgiba, Cumming, Naganathan & Mudla, 2010). According to a projection by the United Nation, Malaysia will achieve the status of a full ageing nation by 2030 when 15% of the population is classified as senior citizens (Hairi et al., 2010; Abd Mutalib, Ismail & Miskiman, 2020).

Along with ageing, the body functions deteriorate and subsequently lead to multi-morbidities. To manage the symptoms and/or to treat these multi-morbidities, there is a higher risk of the usage of many medicines known as polypharmacy (Mortazavi et al., 2016). Polypharmacy is defined as the use of a large number of medications, commonly considered as five or more (Mortazavi et al., 2016). In a study in a university hospital in Malaysia, polypharmacy was further worsened with an increment in age, morbidity, usage of over-the-counter (OTC) drugs, female and the use of cardiovascular, endocrine and musculoskeletal drugs (Senik, 2006). It has been stated that patients using two drugs experience a 13% higher risk of drug-drug interactions (DDIs) and/or adverse drug reactions (ADRs), which increase to 38% when four drugs were taken and to 82% when taking seven or more drugs at the same time (Gallagher, Barry & O'Mahony, 2007). Furthermore, DDI and/or ADR were frequently misinterpreted as the onset of another medical condition in those older patients. An example of ADR is extrapyramidal symptoms (EPS) induced by metoclopramide could be misdiagnosed as the onset of Parkinson's disease, although this misdiagnosis would be less likely in young patients as Parkinson's disease is uncommon in a younger population (Kalisch, Caughey, Roughead & Gilbert, 2011). This could lead to prescribing cascade among elderly in which additional drug(s) is being prescribed to treat the DDI and/or ADR of another drug(s) which then cause polypharmacy (Hilmer, 2008). Hence, potentially inappropriate medications (PIMs) are more likely to be prescribed in this age group. Close monitoring and rational pharmacotherapy are needed when prescribing to this vulnerable group either in terms of dose, frequency or duration.

PIMs can be defined as “medications in which the risks outweigh benefits where there is a safer or more effective alternative therapy for the same conditions” (Galli, Reis, & Andrzejevski, 2016; Hefner et al., 2015). This definition of PIMs has been applied in various settings using a list of explicit criteria, such as the screening tool of older people's prescriptions (STOPP) criteria (O'Mahony et al., 2015) and Beers criteria (Fick et al.,2019). Beers criteria were first compiled by Dr Mark H. Beers, a geriatrician based on a consensus panel of experts by Delphi method on 1991, initially focused exclusively on nursing home residents. The function of the criteria is to identify potentially high-risk medications used by older people. Due to factors such as local prescribing practises and formularies, these instruments differ in their ability to distinguish PIMs in various healthcare settings. There is a systematic review on comparing applicability and sensitivity of STOPP and 2002 version of Beers Criteria. Six studies obtained were investigated and concluded that STOPP is more sensitive than the 2002 Beers Criteria (Hill-Taylor et al., 2013). However, on a more recent study shows that the 2012 version of Beers criteria identified more PIMs compared to STOPP criteria (Oliveira et al., 2015). The updated version includes drugs that should be avoided or should have their dose adjusted based on individual kidney functions and selected drug-drug interactions. It has been used widely in geriatric clinical care, education, research and in the development of quality indicators (Radcliff et al., 2015). With a long history and its development in 1991, Beers criteria were frequently updated in 1997, 2003, 2012, 2015 and most recently in 2019 by the American Geriatrics Society (AGS) (Fick et al.,2019). In contrary, STOPP criteria are only in version 2 in 2015 after its development in 2008 (O'Mahony et al., 2015).

PIMs used in the elderly is associated with an increased risk of DDIs and/or ADRs (Galli et al., 2016; Hefner et al., 2015). A systematic review conducted by Xing et al. (2019) in investigating associations between PIMs exposure and adverse events, such as ADRs, hospitalisation, and mortality. Despite no significant association between mortality and PIMs, a statistically significant correlation between ADRs and hospitalisations with PIMs was found in the combined study. A previous study shows that PIMs such as non-steroidal anti-inflammatory drugs (NSAIDs) had been associated with adverse outcomes and increase the cost of hospitalisation (Galli et al., 2016). Thus, it is crucial to identify the PIMs to reduce DDI and/or ADR in older patients. By concept analysis, deprescribing may lead to cost reduction in terms of reduced medications, reduced hospitalisation and improved adherence as having less medication to monitor (Page, Clifford, Potter, & Etherton-Beer, 2018). In the Health Economics of Potentially Inappropriate Medication (HEPIME) study among elderly aged 65 years

old and above in Germany, by controlling for the number of prescribed medicines, the gap in overall healthcare expenses between PIM and non-PIM groups was € 401 (≈MYR 1877.25, as of 2017) in a 3-month period. There is a lack of published study in Malaysia that investigates PIMs in a Malaysian public hospital and incorporating prescription cost analysis among elderly outpatients. Hence, this study aims to determine the prevalence of PIMs by using Beers criteria 2015 and the factors associated with PIMs. This study also compares pharmacotherapy cost associated with PIMs and non-PIMs.

Methods

This study was conducted in a tertiary hospital in Malaysia, Hospital Tuanku Fauziah, the only hospital in the state of Perlis at the time of the study which serves a population of 252,000 during our period of study in 2017 (Department of Statistics Malaysia, 2017). This hospital did not have in-house nor visiting geriatrician. A retrospective study was conducted among clinic outpatients aged more than 65 years old. All clinic prescriptions (prescribed for at least 4 weeks of treatment and must be taken regularly) were collected in a specialist clinic pharmacy from 1st March 2017 to 15th April 2017. The exclusion criteria were referral repeats prescriptions for patients to get the next refills in other healthcare facilities, prescriptions for intravenous and external preparation.

The patients' identifiers were further screened using the Pharmacy Information System (PhIS, Pharmaniaga®, Shah Alam, Malaysia) to include visits to other specialist outpatient clinics. If there were duplicate prescriptions of the same patients, the latest data were considered. The number of medications is defined as the number of types of medication prescribed for the patient using the latest prescriptions and considering all current clinic visits. The Beers 2015 criteria were used to identify and assess any inappropriate prescribing. Any medication categorised under PIM was checked whether it was appropriate for that patient using the PhIS system on history of medication taking and the patient medical record kept in the respective clinic. If the PIM were appropriate, it would be removed as PIM. For example, for proton pump inhibitors, they would be screened if the patient were on prolonged corticosteroids or NSAID use, or diagnosed with erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition. Two researchers examined patients' medications for PIMs used independently and any discrepancies were resolved by consensus from all researchers. The existence of polypharmacy was analysed as one of the independent variables: patients were subjected to polypharmacy when they received more than 5 medications. As pill burden is not in the scope of our study, the number of medications was calculated as the number of active ingredients for any combination drug (multiple active ingredients in a single dosage form) prescribed. Patients were divided into two groups either PIM (prescribed with at least one PIM) or non-PIM (was not prescribed with any PIM) groups.

Prior data indicated that the proportion of outpatients prescribed with at least one PIM (PIM group) was 0.276 (Lim et al., 2016). By considering type I probability error and precision both to be valued at 0.05, we needed to study 308 samples.

The data were analysed using IBM SPSS Statistics for Windows Version 20.0 (IBM Corp, Armonk, NY). For descriptive analysis, categorical data were presented as frequencies and percentage while numerical data were presented as mean and standard deviation (SD) or median and interquartile range (IQR). For inferential analysis, binomial logistic regression was used to study the covariates on the prescribing of PIM. Prescriptions cost comparison was analysed using Mann-Whitney tests as the data were non-parametric. p-values of less than 0.05 were considered as statistically significant. This study was registered with the National Medical Research Registry (NMRR-17-2668-36550) and was approved by the Medical Research Ethics Committee (MREC) Malaysia.

Results

A total of 472 outpatients were analysed in this study. 186 (39.4%) patients were prescribed with at least one PIM while 286 (60.6%) patients were not prescribed with any PIM. The mean age of patients in the PIM group was 73.8 (6.94) while for the non-PIM group was 73.0 (6.31). **Table 1** summarises patient characteristics into PIM and non-PIM groups.

Table 1: Patient characteristics (n=472)

Characteristics	PIM (n=186) n (%)	Non-PIM (n=286) n (%)
Age (years)		
65-70	82 (44.1)	127 (44.4)
71-75	38 (20.4)	72 (25.2)
>75	66 (35.5)	87 (30.4)
Gender		
Male	95 (51.1)	162 (56.6)
Female	91 (48.9)	124 (43.4)
Race		
Malay	144 (77.4)	216 (75.5)
Non-Malay	42 (22.6)	70 (24.5)
Polypharmacy		
No	69 (37.1)	156 (54.5)
Yes	117 (62.9)	130 (45.5)
Number of clinic visits		
1	181 (97.3)	276 (96.5)
> 1	5 (2.7)	10 (3.5)

Among the 472 geriatric patients, the most prescribed PIMs were diuretic, which was prescribed to 74 (15.7 %) patients followed by short and immediate-acting benzodiazepine to 55 (11.7%) patients and proton pump inhibitors to 54 (11.4%) patients, as shown in **Table 2**. A total of 278 PIMs was prescribed to 472 geriatric patients, which turns up to be 0.6 PIMs/geriatric patient. There is an average of 1.5 PIMs prescribed to 186 PIM patients.

Table 2: Types of potentially inappropriate medication (PIM) (n=278) prescribed to sample population (n=472)

PIM prescribed	PIM frequency (%)
Diuretic	74 (15.7)
Short and immediate-acting benzodiazepine	55 (11.7)
Proton pump inhibitor (PPI)	54 (11.4)
Selective serotonin reuptake inhibitor (SSRI)	29 (6.1)
Antipsychotic	21 (4.4)
Peripheral α1 blocker	20 (4.2)
Chlorpheniramine	14 (3.0)
Digoxin	5 (1.1)
Amitriptyline	5 (1.1)
Ticlopidine	1 (0.2)

Table 3: Factors associated with prescribing of potentially inappropriate medication (PIM) by logistic regression

Factors	Odd ratio	*p*-value
Age	1.02 (0.99-1.05)	0.150
Age group		
65-70	1.00 (ref.)	
71-75	0.88(0.54-1.42)	0.591
>75	1.06 (0.69-1.61)	0.803
Gender		
Male	1.00 (ref.)	
Female	1.25 (0.86-1.81)	0.236
Race		
Malay	1.00 (ref.)	
Non-Malay	0.90 (0.58-1.39)	0.636
Polypharmacy		
No	1.00 (ref.)	
Yes	2.04 (1.40-2.97)	< 0.001
Number of clinic visits		
1	1.00 (ref.)	
> 1	1.31 (0.44-3.90)	0.626

Factors being investigated were age, gender, races, the existence of polypharmacy and numbers of visit in different clinics. The number of medications was the only significant covariate ($p<0.001$): patients subjected to polypharmacy had 2.04 higher odd of having PIMs compared to patients who were not (**Table 3**). The median pharmacotherapy cost for PIM group, MYR 29.50 (≈USD 7.53, as of 2017), was not statistically significant ($p=0.735$) compared to the non-PIM group which was MYR 28.50 (≈USD 7.28). Due to this insignificance, cost of unneeded PIM was not further calculated.

Discussions

In our study, the prevalence of being prescribed PIM is 39.4%. Based on the Malaysian Elders Longitudinal Research (MeLOR) cohort study among urban community-dwelling older adults in Malaysia, the prevalence of PIM was 31.8% (Lim et al., 2017). A study in New Zealand regarding the prevalence of PIMs among elderly showed that the rate of at least one PIM being prescribed was 42.7% (Nishtala, Bagge, Campbell, & Tordoff, 2014). In a previous study from tertiary care hospital in India, showed that 29.2% of patients did have at least one PIMs (Shah, Joshi, Christian, Patel & Malhotra, 2016). A study conducted in a university medical centre in Seoul, Korea, among the 25810 outpatients, 7132 (27.6%) did have at least one PIM (Lim et al., 2016). However, the difference in the prevalence of at least one PIM might be due to the difference in study settings, availability of medications, and prescribing pattern (Abdulah et al., 2018).

The most prescribed PIMs in our setting were diuretic (15.7 %), short and immediate-acting benzodiazepine (11.7%) and PPI (11.4%). A study in India also found that the most commonly found PIMs was spironolactone (15.7%) and benzodiazepine (6.4%), while a study in Japan found out that the most common PIMs were histamine-2 (H_2) blocker (20.5%) followed by benzodiazepines (11.4%) (Akazawa, Imai, Igarashi, & Tsutani (2010). However, a study in Korea stated that the most prescribed PIMs were benzodiazepines, specifically alprazolam (11.2%) followed by clonazepam (10.8%) (Lim et al., 2016). Based on Table 4 from Beers criteria, diuretics are classified as PIM use with caution due to worsening or cause a syndrome of inappropriate antidiuretic hormone secretion of hyponatraemia. All benzodiazepines were classified as PIMs which increases the risk of cognitive impairment, delirium, falls, fractures and motor vehicles crash in older adults while proton-pump inhibitors which are classified as PIM, which increases the risk of *Clostridium difficile* infection, bone loss and fractures.

Previous studies have reported an increased risk of PIMs with age, gender, multiple medications and number of co-morbidities. A study from New Zealand showed that older age, being female and European were associated with increased risk of PIMs. In addition, reported from a study in Brazil, increasing in age and being female contributed to increasing the risk of PIMs. In contrast, a study from India and Japan found that age and sex did not contribute to PIMs. A study from Korea found that an increasing number of medications and prescribing doctors were associated

with PIM use. A systemic meta-analysis illustrated that only polypharmacy is positively associated with PIM use among the elderly, which supports the finding of our study (Santos et al., 2015). We observed a close association between PIMs and polypharmacy. This proved that polypharmacy is a factor strongly associated with PIMs as patients received a high number of medications tend to be prescribed with PIM. Furthermore, this study also found out that older age and increased number of comorbidities were associated with increased medication use (Lim et al., 2017). Hence, the result reflects the need for extra monitoring and precautions from all healthcare professionals towards elderly patients who are on polypharmacy.

In public hospitals, Malaysian citizens pay a nominal fee of MYR 5 (≈USD 1.24) for each specialist consultation visit which the cost includes the supply and refill of medication from the pharmacy (Jaafar, 2013). In our study, we only compared the median cost of medication per month based on acquisition cost, which is the direct pharmacotherapy cost on the Ministry of Health Malaysia's budget. The median cost for the PIM group was not significantly different as to the non-PIM group. There might not be many alternatives in the formulary.

Other studies on prescription cost analysis were based on mean monthly prescription expenditure (as paid by patients). In an Indian study, they identified that cost of therapy per month in the PIM group, USD 29.40 (≈MYR 118.06) was higher ($p < 0.01$) than the non-PIM group, USD 19.80 (≈MYR 79.51) (Shah, Joshi, Christian, Patel, & Malhotra, 2016).

In the study conducted in Germany, statutory health insurance covering 1/3 German population: cost for PIM patients, € 118.37 (≈MYR 554.14) was higher ($p<0.001$) than the non-PIM group, € 91.76 (≈MYR 429.57) (Heider et al., 2017). There were several limitations to our study. We did not know the exact indication for each medication that was prescribed to the elderly population. Furthermore, drugs, herbal medicine or supplements from other facilities were not considered. We did not know the exact outcomes of patients caused by PIMs.

Conclusion

This study shows that approximately one in three patients (38.9%) received at least one PIMs, with the common PIMs prescribed were diuretics, short and immediate-acting benzodiazepines and PPIs. Our study also shows that polypharmacy was the only covariate that affects prescribing of PIM(s). The prescribing of PIM did not affect the direct cost of pharmacotherapy in our setting. Pharmacists should conduct periodic medication reviews among elderly with polypharmacy, in collaboration with prescribers.

Acknowledgements

The authors would like to thank the Director-General of Health, Malaysia for his permission to publish this research. We would also like to extend our appreciation to A'tia Hashim (Pharmaceutical Services Programme, Ministry of Health Malaysia), Nor Azlina Bakar (Perlis State Health Department), Othman Warijo as the Hospital Director, Hospital Tuanku Fauziah (HTF), Nik Mah Nik Mat (Department of Pharmacy, HTF) and also Khairul Shakir Ab Rahman (Clinical Research Centre, HTF) for the continuous support in this study.

Conflict of Interest

The authors declare no conflict of interest nor receive any external funding.

References

Abd Mutalib, Z. A., Ismail, M. F., & Miskiman, N. (2020). *Spatial Analysis: Ageing Population of Multi-ethnic in Rural Area, Malaysia*. Proceedings of the 2020 Asia–Pacific Statistics Week, Bangkok, Thailand. Retrieved from https://www.unescap.org/sites/default/files/70_Spatial_Analysis_Ageing_Population_of_Multi-ethnic_in_Rural_Area_Malaysia.pdf

Abdulah, R., Insani, W. N., Destiani, D. P., Rohmaniasari, N., Mohenathas, N. D., & Barliana, M. I. (2018). Polypharmacy leads to increased prevalence of potentially inappropriate medication in the Indonesian geriatric population visiting primary care facilities. *Therapeutics and Clinical Risk Management, 14*, 1591-1597. doi: 10.2147/TCRM.S170475

Akazawa, M., Imai, H., Igarashi, A., & Tsutani, K. (2010). Potentially inappropriate medication use in elderly Japanese patients. *American Journal of Geriatric Pharmacotherapy*, *8*(2), 146–160. doi: 10.1016/j.amjopharm.2010.03.005

Department of Statistics Malaysia. (2017). *Current population estimates, Malaysia*, 2016–2017. Putrajaya: Malaysia.

Fick, D. M., Semla, T. P., Steinman, M., Beizer, J., Brandt, N, Dombrowski, R., … Flanagan, N. (2019). American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *67*(4), 674-694.

Gallagher, P., Barry, P., & O'Mahony, D. (2007). Inappropriate prescribing in the elderly. *Journal of Clinical Pharmacy and Therapeutics*, *32*(2), 113-121.

Galli, T. B., Reis, W. C., & Andrzejevski, V. M. (2016). Potentially inappropriate prescribing and the risk of adverse drug reactions in critically ill older adults. *Pharmacy Practice (Granada)*, *14*(4), 818.

Hairi, N. N., Bulgiba, A., Cumming, R. G., Naganathan, V., & Mudla, I. (2010). Prevalence and correlates of physical disability and functional limitation among community dwelling older people in rural Malaysia, a middle income country. *BMC Public Health, 10*(1), 492.

Hefner, G., Stieffenhofer, V., Gabriel, S., Palmer, G., Müller, K.-M., Röschke, J., & Hiemke, C. (2015). Side effects related to potentially inappropriate medications in elderly psychiatric patients under everyday pharmacotherapy. *European Journal of Clinical Pharmacology, 71*(2), 165-172.

Heider, D., Matschinger, H., Meid, A. D., Quinzler, R., Adler, J.-B., Günster, C., . . . König, H.-H. (2017). Health service use, costs, and adverse events associated with potentially inappropriate medication in old age in Germany: retrospective matched cohort study. *Drugs & Aging, 34*(4), 289-301.

Hilmer, S. N. (2008). The dilemma of polypharmacy. *Australian Prescriber*, *31*, 2-3.

Hill-Taylor, B., Sketris, I., Hayden, J., Byrne, S., O'sullivan, D., & Christie, R. (2013). Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *Journal of Clinical Pharmacy and Therapeutics*, *38*(5), 360-372.

Jaafar S. N. K., Muttalib, K., Othman, N. H., & Healy, J. (2013). Malaysia health system review. *Health Systems in Transition, 3(1).* New Delhi: World Health Organization, Regional Office for the Western Pacific.

Kalisch, L. M., Caughey, G. E., Roughead, E. E., & Gilbert, A. L. (2011). The prescribing cascade. *Australian Prescriber*, *34*,162-6.

Guzmán, J. M., Pawliczko, A., & Beales, S. (2018). *Ageing in the twenty-first century: A celebration and a challenge.* New York: United Nations Population Fund (UNFPA).

Lim, L. M., McStea, M., Chung, W. W., Azmi, N. N., Aziz, S. A. A., Alwi, S., … Rajasuriar, R. (2017). Prevalence, risk factors and health outcomes associated with polypharmacy among urban community-dwelling older adults in multi-ethnic Malaysia. *PLoS One, 12*(3), e0173466.

Lim, Y. J., Kim, H. Y., Choi, J., Lee, J. S., Ahn, A. L., Oh, E. J., . . . Kweon, H. J. (2016). Potentially Inappropriate Medications by Beers Criteria in Older Outpatients: Prevalence and Risk Factors. *Korean Journal of Family Medicine, 37*(6), 329-333. doi: 10.4082/kjfm.2016.37.6.329

Mortazavi, S. S., Shati, M., Keshtkar, A., Malakouti, S. K., Bazargan, M., & Assari, S. (2016). Defining polypharmacy in the elderly: a systematic review protocol. *BMJ Open, 6*(3), e010989.

Nishtala, P. S., Bagge, M. L., Campbell, A. J., & Tordoff, J. M. (2014). Potentially inappropriate medicines in a cohort of community-dwelling older people in New Zealand. *Geriatrics & Gerontology International, 14*(1), 89-93. doi: 10.1111/ggi.12059

O'mahony, D., O'sullivan, D., Byrne, S., O'connor, M. N., Ryan, C., & Gallagher, P. (2015). STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age and Ageing, 44*(2), 213-218.

Oliveira, M. G., Amorim, W. W., Jesus, S. R., Heine, J. M., Coqueiro, H. L., & Passos, L. C. S. (2015). A comparison of the Beers and STOPP criteria for identifying the use of potentially inappropriate medications among elderly patients in primary care. *Journal of Evaluation in Clinical Practice, 21*(2), 320-325.

Page, A., Clifford, R., Potter, K., & Etherton-Beer, C. (2018). A concept analysis of deprescribing medications in older people. *Journal of Pharmacy Practice and Research*, *48*(2), 132-148.

Radcliff, S., Yue, J., Rocco, G., Aiello, S. E., Ickowicz, E., Hurd, Z., Samuel M.J. & Beers, M. H. (2015). American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *63*(11), 2227-2246.

Santos, A. P., da Silva, D. T., dos Santos Junior, G. A., Silvestre, C. C., Nunes, M. A., Lyra, D. P., Jr., & Antoniolli, A. R. (2015). Evaluation of the heterogeneity of studies estimating the association between risk factors and the use of potentially inappropriate drug therapy for the elderly: a systematic review with meta-analysis. *European Journal of Clinical Pharmacology, 71*(9), 1037-1050. doi: 10.1007/s00228-015-1891-2

Senik, S. (2006). A study of polypharmacy and its associated factors among elderly patients in Klinik Rawatan Keluarga Hospital Universiti Sains Malaysia in 2005. *Malaysian Journal of Medical Sciences*, *13*(1): 79–96.

Shah, K. N., Joshi, H. M., Christian, R. P., Patel, K. P., & Malhotra, S. D. (2016). Prevalence of potentially inappropriate medications and prescription cost

analysis among older cardiac patients in an outpatient department of a tertiary care hospital in India. *Journal of Basic and Clinical Pharmacy*, *7*(4), 110-115. doi: 10.4103/0976-0105.189434

Xing, X. X., Zhu, C., Liang, H. Y., Wang, K., Chu, Y. Q., Zhao, L. B., Jiang, D. C., … Yan, S. Y. (2019). Associations between potentially inappropriate medications and adverse health outcomes in the elderly: a systematic review and meta-analysis. *Annals of Pharmacotherapy*, *53*(10), 1005–1019. doi: 10.1177/1060028019853069