EVALUATION OF POTENTIALLY INAPPROPRIATE PRESCRIBING AMONG HOSPITALISED GERIATRIC PATIENTS: PREVALENCE, PREDICTORS, ASSOCIATION WITH QUALITY OF LIFE AND IMPACT OF A MULTIFACETED INTERVENTION ON HEALTHCARE PROVIDERS' KNOWLEDGE AND PRACTICE IN SELECTED PAHANG HOSPITALS

BY

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ABSTRACT

Background: Potentially inappropriate prescribing (PIP) is a global phenomenon among geriatric patients. The term PIP refers to either potentially inappropriate medication (PIM) or potentially prescribing omission (PPO). PIP is an underestimated problem in Malaysia with a paucity of published data in regards to this issue. Methods: This is a pre-test versus post-test interventional study. The pre-intervention phase was a cross-sectional study that evaluated the prevalence of PIP among hospitalised geriatric patients upon admission and its association with the patients' health-related quality of life (HRQOL). The impact of hospitalisation on PIP was also assessed by comparing the prevalence of PIP before and after the hospitalisation. A multifaceted intervention consisted of academic detailing and a smartphone app. (Plus65 Med©) was delivered to hospital healthcare providers (HCPs), namely physicians and clinical pharmacist. The impact of this intervention on HCPs' knowledge and practice regarding PIP was then assessed. Results: The study found that 58.5% of the involved patients had at least one PIP on admission as identified by the STOPP/START criteria version 2. The most common PIMs were medications that increase risk of falls, and those used in patients with persistent postural hypotension; the use of full dosage of proton pump inhibitors for more than 8 weeks in patients with uncomplicated peptic ulcer and the use of metformin in patients with creatinine clearance < 30 mL/min. The most common PPOs were; the omission of vitamin D supplements in patients with a history of falls, angiotensin-converting enzyme (ACE) inhibitors in patients with documented coronary artery diseases (CAD), heart failure or in diabetic patients with renal failure. No association was found between the presence of PIM (or PPO) with any aspects of the patients' HRQOL. Hospitalisation significantly reduced the prevalence of PIMs from 33.3% at admission to 27% at discharge ($p = 0.004$) but it did not affect the PPOs. No significant changes found in the overall prevalence of PIPs and pattern of PIM or PPO, where hospitalisation did not significantly reduce the prevalence rates of any of individual STOPP or START criteria. Majority of hospital HCPs (67.1%) had inadequate knowledge coupled with low confidence regarding prescribing in geriatric patients, and participants who rated themselves as more confident in prescribing for geriatric patients had significantly higher knowledge scores than those with less confidence ($p = 0.02$). It was found that 60% of the respondents had never heard of geriatric-specific prescribing criteria and only 7.3% of them had ever used such criteria. Lack of formal education on prescribing for the elderly was cited by 78% of the participants as real barrier to appropriate prescribing in geriatric patients. The multifaceted intervention was effective in increasing the overall HCPs' knowledge score ($p = 0.007$) and the number of HCPs who scored above the median point ($p = 0.001$). Moreover, the intervention significantly reduced the prevalence of PPOs among discharged patients ($p = 0.015$) and the two most common PPOs that were seen before intervention (i.e., omission of vitamin D and ACE inhibitors) were significantly lower in the intervention group ($p_1 = 0.001$ and $p_2 = 0.03$). However, the intervention did not significantly affect the prevalence or pattern of PIMs. Conclusion: The study showed that the applied intervention reduced the inappropriately omission of beneficial medications which might have a significant clinical impact on the patients by reducing the incidence of new fractures and by preventing the recurrence of CAD events.

خلاصة البحث

إن الوصف غير المناسب (و.غ.م) للأدوية هو أمر شائع عند المسنين، وهذه الظاهرة لم تحظَ بالدراسة الكافية في ماليزيا. تحرّت هذه الدراسة نسبة انتشار الـ (و.غ.م) عند المرضى المسنين المسعَفين إلى المشفى وتأثير هذا على مستوى جودة حياتهم وكذلك تأثير الاستشفاء على هذه الظاهرة إضافة إلى قياس مدى معرفة الطاقم الطبي للوصف المناسب للأدوية عند المسنين. وجدت الدراسة أن 58.5% كان لديهم و.غ.م واحد على الأقل عند دخول المشفى وذلك بحسب النسخة الثانية من معايير STOPP/START. أكثر أدوية وصفت بشكل غير مناسب كانت الموسّعات الوعائية عند مرضى هبوط الضغط الانتصابي، ومثبطات مضخة البروتون لأكثر من ثمانية أسابيع، والميتفورمين عند مرضى تصفيتهم الكلوية أقل من 30 مل/د. بينما كان أشهر الأدوية التي حذفت بشكل غير مناسب الفيامين د عند المرضى الذين لديهم تاريخ سقوط، وحذف مثبطات الخميرة المحولة للأنجيوتنسين عند مرضى الشرايين الإكليلية أو مرضى السكري المصاحب لأذية كلوية. لم يكن هناك ارتباط بين الـ و.أ.غ و مستوى جودة حياة المرضى. خفض الاستشفاء من وصف الأدوية غير المناسبة من 33.3% إلى 27% ($p = 0.04$) لكنه لم يؤثر على حذف الأدوية المناسبة. وجدت الدراسة أن 67.1 من أفراد الطاقم الطبي لديهم معرفة متواضعة مع ضعف ثقة حول وصف الأدوية للمسنين، وكان هناك ارتباط وثيق بين درجة الثقة ومدى المعرفة ($p = 0.02$). أيضا 60% من المشاركين لم يسمعوا عن المعايير الخاصة بوصف الأدوية عن المسنين مثل Beers وSTOPP/START وفقط 7.3% منهم استخدموا مثل هذه المعايير في حياتهم. أشار 78% من المشاركين إلى أن نقص التعليم والتدريب الرسميين حول الأدوية عند المسنين هو أحد العوائق نحو وصف الأدوية بشكل مناسب عند هذه الفئة العمرية. قمنا بتطوير تطبيق للهاتف الجوال يحوي معاييرSTOPP/START واسميناه Plus65) (©Med ومن ثم قدمناه للطاقم الطبي في المشفى مع سلسلة من المحاضرات التعليليمة حول وصف الأدوية عند المسنين. تم تقييم فعالية هذه المداخلة على معرفة وممارسة الطاقم الطبي. أثبتت المداخلة فعاليتها في تحسين معرفة الطاقم الطبي حول الوصف المناسب للأدوية عند المسنين ($p = 0.007$) وكذلك كانت فعالة في التخفيف من حذف الأدوية المناسبة ($p = 0.015$) وخصوصاً تلك التي كانت منتشرة بكثرة قبل المداخلة لكن المداخلة لم تنجح في خفض وصف الأدوية غير المناسبة. بالمحصلة: إن المداخلة المجراة زاد من وصف بعض الأدوية المفيدة للمرضى والتي قد تقيهم من حدوث كسور جديدة أو حوادث قلبية إكليلية في المستقبل.

APPROVAL PAGE

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DECLARATION

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC-CCI	Age combined Charlson Comorbidity Index
ACE	Angiotensin-converting enzyme
ADL	Patients' activities of daily living
ADR	Adverse drug reaction
App	Application
ARB	Angiotensin receptor blocker
BCW	Behaviour change wheel
CAD	Coronary artery diseases
CCB	Calcium channel blocker
CDSS	Clinical decision support software/computerised decision support system
CGA	Comprehensive geriatric assessment
CGE	Continuous medical education
COM-B	Capability, opportunity and motivation behaviour
CMR	Clinical medication review
CPOE	Computerised physician/prescriber order entry
CRC	Clinical Research Center
DRP	Drug related problem
EUGMS	European Union Geriatric Medicine Society
GABA	Gamma-aminobutyric acid
GP	General practitioners
HCP	Healthcare provider/professionals
HMR	Home medication review
HRQOL	Health-related quality of life
I-CVI	Content validity index for items
INR	International normalized ratio
IQR	Interquartile range
IT	Information technology
MAI	Medication appropriateness index
MDT	Multidisciplinary team
NSAIDs	Nonsteroidal anti-inflammatory drugs
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescribing
PPI	Proton pump inhibitor
PPO	Potentially prescribing omission
QoL	Quality of life
RCT	Randomised controlled trial
S-CVI/Ave	Average content validity index for scale
SD	Standard deviation
SPRM	Structured pharmacist review of medication
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Elderly Persons' potentially inappropriate Prescription
TCA	Tricyclic antidepressants

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

The use of medication consists of five consecutive steps; prescribing, communicating orders, dispensing, administering, and monitoring. Errors associated with potential risks may occur at each step, and several preventable actions can be taken at prescribing level where medications might be prescribed inappropriately (Page et al., 2010). Inappropriate prescribing is demonstrated to be associated with adverse drug reactions (ADRs) (Hamilton et al., 2011), increase in hospitalisation (Dalleur et al., 2012; van der Stelt et al., 2016), decrease in patients' adherence (Mansur et al., 2009), and healthcare resource wastage (Cahir et al., 2014; Morgan et al., 2016).

Potentially inappropriate prescribing (PIP) occurs when there is a prescribing of a potentially inappropriate medication (PIM), where the risks associated with the medication outweigh the expected benefits, or when there is a potentially prescribing omission (PPO), where a specific medication is indicated but not prescribed (Hill-Taylor et al., 2016; O'Connor, Gallagher, & O'Mahony, 2012).

The mean age of the global population is consistently increasing as the quality of health services keeps on improving. It is expected that the number of elderly people will reach more than 70 million by 2030 which is double that recorded in 2000 (Amanda H. Lavan, Gallagher, & O'Mahony, 2016). Alarmingly, inappropriate prescribing is quite common among elderly people whom are the largest consumers of medications (Jetha, 2015). These people are more vulnerable to drug-related problems (DRPs) and negative outcomes associated with inappropriate prescribing due to the presence of multiple

comorbidities, polypharmacy and age-related pharmacokinetic and pharmacodynamic alterations (O'Connor et al., 2012).

1.2 DEFINITION OF THE ELDERLY PERSON

In fact, there is no consensus definition for elderly people. The UN agreed cutoff is 60+ years to refer to the elderly people. As the age of 60 or 65 is the retirement age in most countries, it was stated that this age is the beginning of old age. Most developed countries have stated the chronological age of 65 years as a definition of "elderly" or elderly person (UNPFA, 2012). In medical literature, elderly people are conventionally defined as those aged 65 years and over (Patterson, Hughes, Kerse, Cardwell, & Bradley, 2012). As most of the criteria for appropriate prescribing in elderly people were developed to be used in patients ≥ 65 years old (Basger, Chen, & Moles, 2008; O'Mahony et al., 2015; Samuel, 2015), the current study used the age of 65 years old as a cutoff to refer to elderly people. According to the Oxford English dictionary, the word "geriatric" is a noun and adjective that means older person or relating to older people, especially with regard to their healthcare (Simpson & Weiner, 1989). In the current study, the term "elderly people" was used to refer to general people who are ≥ 65 years old, and the term "geriatric patients" was used to refer to patients who are ≥ 65 years old.

1.3 CHANGES WITH AGEING

1.3.1 Changes in Pharmacokinetics of Drugs in Elderly People

Realisation of pharmacokinetic differences of medications is essential to design a proper drug dosing regimen for every patient. Age-related changes in all phases of drug pharmacokinetics should be taken into consideration when prescribing for geriatric

patients. These changes are results of reduced functions of several organs and decreased ability of homeostatic mechanisms with age (Corsonello, Pedone, & Incalzi, 2010).

1.3.1.1 Absorption

Several changes were reported to occur in the gastrointestinal (GI) tract with advancing age that may account for alterations in the rate and extent of drug absorption. In elderly people, gastric acid production decreases which results in increased gastric pH. In addition, salivation, absorption surface area, splanchnic blood flow, small intestine's absorptive capability, peristalsis, gastric emptying and colonic transit are all decreased with advancing age (Corsonello et al., 2010; Duraković & Vitezić, 2013).

Regardless of the relatively large number of age-related changes in the GI tract, a limited number of drugs are affected by these changes. This is due to the fact that most drugs are absorbed by passive transport which is not affected by the mentioned changes. However, age-related altered absorption may be clinically important. For example, the bioavailability of some antiepileptic drugs may be influenced by advancing age resulting in altered plasma concentrations of these narrow-therapeutic index agents (Gidal, 2006). On the other hand, decreased first-pass effect associated with advancing age results in increased bioavailability of morphine and some other drugs (Emily R. Hajjar et al., 2014). Decreased gastric emptying and colonic transit lead to delayed absorption of most drugs. This change may be of importance when fast onset and early achievement of maximum concentration are required. However, it has no clinical effect on chronic medications once the steady state concentration is achieved.

1.3.1.2 Distribution

Total body fat increases, whilst muscle (lean body) mass and total body water decrease in elderly people. Therefore, the volume of distribution of lipophilic drugs (e.g., diazepam) increases resulting in possible prolonged half-life and extended clearance of these medications (Hutchison & O'Brien, 2007). Additionally, this may reduce the availability of some drugs that excessively distribute to fat tissue (e.g., vitamin D) in the circulating blood. Reduced vitamin D may put geriatric patients -particularly women- at higher risk for negative clinical consequences like fractures (Corsonello et al., 2010). On the other hand, hydrophilic drugs (e.g., aminoglycosides) have a smaller volume of distribution in elders compared with younger people which result in an increase in their plasma concentration and thus lower than normal loading dose may be required (Corsonello et al., 2010; Emily R. Hajjar et al., 2014).

Plasma albumin levels also reduce in geriatric patients - particularly acutely ill patients- which increases free (unbound) fraction of acidic medications (e.g., warfarin) that highly bound to plasma albumin (Duraković & Vitezić, 2013). As the free fraction of a drug is the responsible fraction for the pharmacological effects, increasing unbound drug concentration may increase side effects and toxicity of highly protein-bound drugs (Duraković & Vitezić, 2013; Hutchison & O'Brien, 2007). However, in such cases, the body usually increases the clearance of these drugs as a compensating mechanism to avoid harmful effects of the increased pharmacological action (Emily R. Hajjar et al., 2014). This makes the age-related albumin change clinically insignificant except during early stage of drug therapy until drug's steady-state equilibrium takes place. In addition, this issue should be taken into consideration when interpreting of free concentrations of such drugs (Hutchison & O'Brien, 2007). Basic medications (e.g., imipramine) bind in the human body to α1-acid glycoprotein which increases in elderly people. This reduces

the concentration of the free drug and may lessen the pharmacological effects of some basic drugs (Hutchison & O'Brien, 2007).

P- glycoprotein is a cell membrane active efflux pump that contributes to the active drug transportation. There is evidence of reduction of P- glycoprotein activity in elderly people which notably influences the drug transportation across the blood-brain barrier (BBB). This exposes the brain of elderly people to higher than normal amount of medications leading to accumulation of medications in the brain and greater cerebral side effects (Corsonello et al., 2010; Emily R. Hajjar et al., 2014).

1.3.1.3 Metabolism

There are decreases in liver volume and hepatic blood flow by up to 30% and 50%, respectively in elderly people (Corsonello et al., 2010; Hutchison & O'Brien, 2007). Bioavailability of medications that undergo extensive first-pass metabolism (e.g. morphine and verapamil) may significantly increase and therefore, lower than normal doses should be used (Hutchison & O'Brien, 2007). In contrast, the bioavailability of prodrugs like some angiotensin converting enzyme (ACE) inhibitors decreases in geriatric patients as these medications need the first pass metabolism to be converted into active ingredients (Corsonello et al., 2010). Phase I reactions (oxidation, reduction and hydrolysis) are more diminished with age than phase II reactions. It is believed that the reduction in phase I metabolism is more attributed to the decrease in liver mass than to the reduced enzyme activity. The clearance of medications that extensively metabolised by phase-I reactions like diazepam and theophylline, decreases and their half-lives increase, so their doses need to be lowered (Emily R. Hajjar et al., 2014). As phase II metabolism is not significantly affected with age, medications that are

metabolised mainly through this pathway are considered as safer alternatives in geriatric patients compared to those extensively metabolised by phase I reactions.

1.3.1.4 Elimination

Advancing age associates with an impaired renal function which is related to the reduction in kidney mass, renal blood flow and glomerular filtration in elderly people. However, it is difficult to distinguish between the effect of advancing age per se on renal function and the impact of age-related diseases and polypharmacy. These changes reduce the elimination of medications that extensively excreted by the kidneys (e.g., aminoglycoside, ACE inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) digoxin, lithium, and vancomycin). Therefore, the half-lives of these medications are prolonged which leads to an increase in the incidence of ADRs in geriatric patients (Corsonello et al., 2010; Emily R. Hajjar et al., 2014; Mangoni & Jackson, 2003)

Creatinine clearance serves as a representative of renal glomerular filtration and hence it is considered as an indicator of the renal function. No specific formula is established for elderly people to calculate their creatinine clearance. Although several equations were proposed for calculating creatinine clearance, Cockcroft Gault equation (Cockcroft & Gault, 1976) is still the standard formula for dose adjustment of renaly-eliminated drugs in elderly people (Emily R. Hajjar et al., 2014; Hutchison & O'Brien, 2007):

$$\text{Creatinine Clearance (mL/min)} = \frac{(140-age)x\ weight\ (kg)}{serum\ creatinine\ (\frac{\mu mol}{L})}\ x\ constant$$

Where: The constant is 1.04 for females and 1.23 for males.

For obese patients (patients with body mass index ≥ 30), it is suggested to use the lean body weight since muscles are the source of creatinine in the body. Another

option is to use Salazar Corcoran formula (Salazar & Corcoran, 1988) for calculating creatinine clearance for obese people.

1.3.2 Changes in Pharmacodynamics of Drugs in Elderly People

Ageing is associated with pharmacodynamic changes that may clinically affect the therapeutic response to several medications independently of age-related pharmacokinetic alterations. In contrast to pharmacokinetic changes, pharmacodynamic changes could not be predicted or quantified (Corsonello et al., 2010). The changes in drug response in geriatric patients may be due to changes in number and affinity of receptors, post-receptor signal transduction and deterioration in homeostatic response in geriatric patients (Emily R. Hajjar et al., 2014). These pharmacodynamic changes - in addition to pharmacokinetic alterations- further complicate the prescribing in geriatric patients. Various body systems are affected by these changes, and therapeutic adjustment may be required in certain cases.

1.3.2.1 Central Nervous System

Multiple physiological changes occur in the brain of elderly people. These changes are complex and involve different regions of the brain by different mechanisms including alteration in the number of neurons and receptors, changes in the neurotransmitters and hormonal shifts (gender and growth hormones). Additionally, age-related impairment of BBB permeability increases the concentration of many drugs in the brain. Changes in medications that affect gamma-aminobutyric acid (GABA), cholinergic and dopaminergic systems in the brain are the most prominent and studied medications (Corsonello et al., 2010; Hutchison & O'Brien, 2007).

1.3.2.1.1 Changes of Responsiveness to Benzodiazepines

The exact mechanism of increased effect of benzodiazepines in elderly is unclear (Corsonello et al., 2010; Mangoni & Jackson, 2003). A proposed mechanism is the age-related changes in the GABA system which may increase the sensitivity of geriatric patients to benzodiazepines (Hutchison & O'Brien, 2007). For instance, it was found that the half maximal effective concentration (EC50) of midazolam and flunitrazepam in elderly people is half of that in young adults regardless the absence of pharmacokinetic changes of these medications with age (Corsonello et al., 2010). Therefore, geriatric patients are at higher risk to experience ADRs of benzodiazepines. This is clinically significant as the aggravated hypnosedative effect of benzodiazepines is associated with falls and consequently hip fractures (de Jong, Van der Elst, & Hartholt, 2013).

1.3.2.1.2 Changes in Responsiveness to Cholinergic Medications

Several changes in the cholinergic system have been reported to be associated with advancing age. There is a decrease in 1) number of cholinergic neurons; 2) choline uptake from the periphery; 3) choline acetyltransferase levels and 4) cholinergic receptors. Also, the levels of acetylcholinesterase are increased (Hutchison & O'Brien, 2007). These alterations lead to increase the CNS sensitivity to the anticholinergic effects of medications such as sedation, drowsiness, urinary retention, constipation, tachycardia, and confusion. Widespread drug classes are demonstrated to have anticholinergic effects like antispasmodics, bronchodilators, antihistamines, skeletal muscle relaxants, and antipsychotic drugs (Collamati et al., 2016). Because of that, the anticholinergic burden should be considered when prescribing multiple drugs with anticholinergic effects for geriatric patients.