



Inappropriate prescription in older adults: A review

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Abstract

Drug therapies in elderly people are difficult to manage for different patient-related and drug-related factors. Hence, elderly people are prone to be prescribed with inappropriate medications. Different approaches have been developed so far to optimize the therapy in elderly people. The most widely studied and used are the explicit criteria. Results from the prospective and retrospective studies based on explicit criteria suggest a high prevalence of inappropriate prescribing in the global elderly population. Numerous predictors of inappropriate prescribing have also been identified so far however; the studies do not comply with each other. Furthermore, observational studies on health-related events associated with the inappropriate prescription in geriatrics suggest a need of timely implementation of appropriate interventions including involvement of clinical pharmacists during a drug utilization review, multidisciplinary approach for therapy optimization, continuing education to physicians, computer-based therapeutic support systems and so on.

Keywords: Inappropriate prescription, PIM, Beers criteria, STOPP/START

Introduction

In recent years, the life expectancy of people has been continuously increasing. The older people are living longer days than in previous years. It has been estimated that in 2050 the population of older people will nearly be doubled ^[1]. Although the elderly population accounts for only a small portion of the total population, health care and drug consumption are two to three times that of the adults ^[2]. People with advanced age contribute to one-third of the total healthcare cost ^[3]. With this, it becomes necessary to preserve and properly manage the health and wellbeing of the elderly, so that the remaining years are spent with comfort. However, managing elderly patients is not an easy and simple task. Generally, with the increasing age, there is an alteration in the physical, psychological, and physiological status of patients. Moreover, pharmacokinetics and pharmacodynamics of the same drug differ between adult and elder population. A safe drug in adult people may produce serious adverse effects in elderly patients. The risk-benefit profile is further worsened by multiple comorbidities, dementia, frailty, and functional status ^[3]. The presence of multiple diseases warrants for the need for multiple prescriptions leading to polypharmacy and hence a complex therapeutic regimen ^[4]. Study shows that one-half of the geriatric patients have been consuming five or more medications ^[5]. There are numerous components of prescribing in elderly people which include determining indications for drug use, choosing the most appropriate drug, determining dose and frequency, routine or continuous monitoring of therapy, and patient education.

Inappropriate prescribing

Drug-related harm is a serious concern for health

professionals when treating patients. A systematic review and a multicenter prospective trial have determined that drug-related harm is present in 0.4 to 51.2% of patients, 35 to 59% of which could be prevented [6, 7]. This indicates that, unless proven otherwise, any symptoms appearing in the elderly should be considered as drug-induced. Inappropriate prescribing refers to the physicians' improper choice of medication. In simple, a medication with harm outweighing the benefit is prescribed to the patients despite the availability of better alternatives. Moreover, inappropriate prescribing is costly, not supported by evidence and preventable ^[8]. Inappropriate prescribing consists of three forms namely over-prescribing, under-prescribing and mis-prescribing. Over-prescribing is the process of prescribing medication(s) when not indicated. Similarly, Under-prescribing refers to the act of omission of prescription when it is indicated. In the case of mis-prescribing, medication is prescribed when indicated but the choice of drug, dose, dosage, frequency, and drug interactions are beyond standard ^[9]. There is a proportionate relation of advancing age with the inappropriate prescription finally leading to increased adverse reactions, morbidity and mortality ^[10].

Inappropriate prescribing is one of the reasons for prescribing cascade. In prescribing cascade, an adverse effect to a drug is misdiagnosed as a newly developed disease to which a new medication is prescribed. The new medication is accumulated inside the body and sometimes may lead to a generation of symptoms of adverse effect which is again mistook with another disease ^[11]. Prescribing cascade is common to those drugs whose symptoms of side effects are similar to the symptoms of common diseases. Some examples include anti-Parkinson therapy to alleviate symptoms arising from

antipsychotics [12] and treatment of urinary incontinence associated with the use of cholinesterase inhibitors using anticholinergic drugs [13].

In most instances, adverse events may be dose-related. This is the case when normal doses are used for patients residing in long-term care settings and patients with impaired renal function. Since renal diseases are common in geriatric patients, dose adjustments become necessary. With reduced muscle mass in older patients, available formulas that can be used to measure renal insufficiency in many cases may provide false-negative results [14]. In long-term care settings, antipsychotics and warfarin are the most common drugs producing adverse events. There is an increased likelihood of falls, fractures and deaths of the elderly with antipsychotics used for behavioral and psychological symptoms (BPSD). Similarly, unmonitored use of warfarin may increase the risk of bleeding [15].

The Drug Burden Index is a method of simulating the impact of a total number of drugs prescribed, drugs with anticholinergic and sedative-hypnotic effects, and the daily doses of the drugs on the patient's physical and cognitive functions. Increased drug burden index has been linked with decreased functional status and increased risk of falls [16, 17]. Anticholinergics have drawn the particular attention of the geriatricians and the guideline makers. The reason being the higher susceptibility of aged people to adverse reactions of anticholinergic drugs. The most common adverse effects of anticholinergic drugs in elderly patients include blurred vision, confusion, dry mouth, memory loss, constipation, hallucinations, tachycardia, impaired sweating, and urinary retention. Anticholinergics may precipitate urinary retention in elderly patients with benign prostatic hyperplasia. Previous literature has identified an increased risk of pneumonia associated with anticholinergics [18].

Measurement of inappropriate prescribing

The process and the outcome measures can be used to assess inappropriateness in a prescription. The process and outcome measures are further divided into explicit and implicit types. Process measures assess performance and behavior quality, while outcome measures assess health-related outcomes that are secondary to inappropriate prescription. Explicit criteria are based on available evidence and are prepared based on published literature, and expert opinions and consensus. Explicit criteria consist of drug or disease-oriented recommendations for appropriate practice. Any violation of the recommendations will lead to inappropriateness. Explicit criteria can be used to evaluate over-prescribing, under-prescribing, and mis-prescribing. However, in this approach, the patient's comorbidity status and preferences are not given any importance. The implicit approach is the process where the clinicians and experts based on their knowledge and available evidence make clinical judgments on the appropriateness of prescription. Here, the patient's preferences and the comorbid status are well respected during the evaluation. Unlike explicit criteria, the prime focus of judgment in implicit criteria is patients rather than disease or drug. However, implicit methods are very time consuming and dependant on the knowledge, attitude and practice of the

physicians.

Numerous explicit criteria have been developed. A systematic review has reported a total of 36 explicit criteria published till 2017 which are: five versions of Beers criteria (version 1991, version 1997, version 2003, version 2012, version 2017), Stuck criteria 1994, McLeod criteria 1997, Zhan criteria 2001, Rancourt criteria 2004, Lindblad criteria 2006, Healthcare Effectiveness Data and Information Set (HEDIS) 2006, French criteria 2007, Japanese Beers criteria 2008, Thailand criteria 2008, two Screening Tool of Older Person's Prescriptions (STOPP) criteria (version 1 2008 and version 2 2015), Norwegian General Practice (NORGEP) criteria 2009, Fit FOR The Aged list (FORTA) 2009, Italian criteria 2010, Priscus criteria 2010, Korean criteria 2010, Passi et al. 2010, Taiwan criteria 2012, Australian criteria 2012, Australian prescribing indicator tools 2012, New Mexico criteria 2012, Czech National criteria 2013, Clyne et al. 2013, Castillo-Paramo criteria 2013, Galan – Retamal criteria 2014, European list of potentially inappropriate medications for older people (EU(7) PIM) list 2015, Norwegian General Practice-Nursing Home (NORGEP- NH) criteria 2015, Kim criteria 2015, Ghent Older People's Prescriptions community Pharmacy Screening (GheOPS) 2016, Mazhar criteria 2017, and Khodyakov criteria 2017. Other criteria not listed in the systematic review are the Assessing Care of Vulnerable Elders (ACOVE) quality indicators, the Improving Prescribing in the Elderly Tool (IPFT), the Winit-Watjania criteria, the Chinese criteria 2017 (Criteria of potentially inappropriate medications for older adults in China) and the Beers criteria version 2019. Most of the earlier criteria developed the potentially inappropriate list (PIM) list based on evidence from the literature whereas, other criteria referenced the earlier criteria and adapted accordingly. The explicit criteria are developed from the consensus from series of the Delphi process, modified Delphi process, RAND/UCLA (Research and Development/University of California, Los Angeles), or Nominal Group technique [19].

Beers criteria and its updates are the most widely referenced and validated explicit criteria used to identify potentially inappropriate medication in elderly patients. The practical usefulness of the Beers criteria for assessing the prescribing quality has been evidenced by the various scientific literature [20]. It was originally developed by Beers and colleagues in 1991 using the Delphi method [3, 9]. To date, there have been five updates of the Beers criteria in different years. Starting from the year 2012, the American Geriatric Society has taken an initiative to update the Beers criteria every three years. Beers 2019 is the fifth and the latest installment of the Beers criteria published by the American Geriatrics Association (AGS). Although the target population of the first version of the Beers criteria were the elderly patients residing in nursing homes, the recent versions can be applied in elderly patients aged 65 years or above in all settings including ambulatory care, acute or long-term care, community-dwelling, institutionalized patients, and primary care settings. However, AGS has refrained the use of the Beers criteria in patients at the terminal stage or those receiving palliative care. This is because the therapeutic goal in these groups may be different from those of other groups. Similar to the Beers 2015 version,

2019 version also consists of recommendations based on different conditions which include: drugs to avoid list in general elderly people irrespective of comorbidity status (30 recommendations); drugs to avoid in elderly with specific diseases (10 recommendations for specific diseases); drugs to use with caution (six recommendations); drug-drug interactions to avoid in general elderly (17 recommendations); and medications to have dosage reduced or avoided in elderly patients based on level of renal function (23 recommendations). Some examples of the recommendations include: nifedipine should be avoided in general elderly owing to its potential for hypotension and risk for precipitation of myocardial infarction; indomethacin should be avoided in general elderly because of increased risk of gastrointestinal bleeding and kidney injury in older adults; avoid use of NSAIDs in patients with chronic kidney disease of stage 4 or higher or patients with creatinine clearance below 30 ml/min owing to the risk of renal toxicity and further renal decline; rivaroxaban and dabigatran should be used cautiously for the treatment of venous thromboembolism and atrial fibrillation to the patients aged over 75 years because of the increased risk of gastrointestinal bleeding; avoid using benzodiazepines simultaneously with opioids because of the increased risk of opioid toxicity, and Ciprofloxacin should be avoided in elderly with creatinine clearance below 30 ml/min owing to the risk of CNS effects and tendon rupture. Besides the above recommendations, a list of anticholinergic drugs has also been provided. To each recommendation, a corresponding strength of recommendation and level of evidence is also supplemented to aid the decision making [21]. As such, the strength of evidence is graded into strong and weak recommendations and the quality of evidence into high, moderate and low levels of quality. In 2015 AGS has also published a list of alternative medicines to Beers 2015 list [22]. Some of the drugs listed in Beers criteria are over-the-counter products. Hence a thorough medication review becomes necessary to identify such inappropriate use.

Another of the commonly used explicit criteria to evaluate the mis-prescribing is the Screening Tool of Older Person's Prescriptions (STOPP) criteria. It was originally developed in 2008 as an alternative to Beers criteria for use in European countries since many of the drugs listed in Beers criteria were not available in Europe. The second and the most recent update is the STOPP version 2 published in 2015. STOPP version 2 includes 80 different recommendations. A notable difference of STOPP criteria compared to Beers criteria is that the STOPP criteria provide enough emphasis on the duplication of medications and medication classes [23]. Along with the STOPP criteria, Screening Tool to Alert doctors to the Right Treatment (START) criteria have also been published, which can be used to assess the under-utilization of the medication. The STOPP criteria have 34 recommendations [23]. Under-utilization can lead to therapy failure in patients. The potential factors that may lead to the underutilization of therapy include the affordability of the therapy [24], clinician incompetence, lack of knowledge and unavailability of the drug and dose.

The Assessing Care of Vulnerable Elders (ACOVE) project is the most comprehensive set of evidence-based quality

indicators used to examine the quality of care provided to vulnerable community-dwelling residents aged 75 years or over. The latest installment is ACOVE 3, consisting of 392 quality-of-care indicators. The indicators are grouped according to 26 different medical conditions. It covers four areas of care for vulnerable elderly patients, including screening and prevention, diagnosis, treatment, and follow-up and continuity. It also provides practical advice to improve appropriate prescription [25].

The Medication Appropriateness Index (MAI) is a well established implicit criterion. In this criterion, clinicians and experts make judgments on ten aspects of a prescription and subsequently rate the level of appropriateness in a 3-point Likert scale (appropriate, marginally appropriate and inappropriate). The drug is finally given a weighted score from 0 to 18, with higher scores indicating lower appropriateness. MAI is applicable to patients with any age group. The ten aspects of a prescription are drug indication, efficacy, drug dosage, correct direction, practical direction, drug-drug interaction, drug-disease interaction, drug repetition, treatment time and cost [26].

Prevalence of PIM

The prevalence of PIM varies with the criteria used to determine the PIM, setting where the studies are conducted and the different regions. Numerous systematic reviews have identified that the majority of the prevalence studies have used Beers criteria as the explicit criteria to evaluate the inappropriateness of prescription in the elderly. A systematic review in community-dwelling patients in Europe found the prevalence of PIM to be 22.6% (range 0% to 98%). The studies included in the systematic review used Beers 2003 and Beers 1997 and STOPP criteria [27]. Another systematic review identified a global prevalence of PIM in community-dwelling elderly to range from 11.5% to 62.5% when using overall explicit criteria [28]. PIM in institutionalized American elderly patients (nursing home residents, patients in residential care facility, patients visiting the emergency department, or hospitalized patients) ranged from 3.6% to 9.2% based on overall criteria [29]. Elderly patients with dementia have PIM ranging from 10 to 74% [30]. In the case of elderly patients residing in long-term care facilities, PIM is present in 18.5% to 82.6% [31]. Elderly nursing home residents have an average PIM prevalence of 26.8% in North America, 43.2% in Europe, and 29.8% in other areas [32]. A 2012 systematic review identified that 20.5% of primary care unit elderly patients had PIM [33].

Predictors of PIM

Several factors may increase the likelihood of a PIM prescription. A wide number of possible predictors have been studied and the possible association has been tested. However, the results from the studies are inconsistent with each other. The results have been found to vary between the countries where the study was conducted, the criteria used for the measurement and the type of setting. The most commonly studied predictors are polypharmacy, age, gender, number of medications prescribed, certain diseases, number of comorbid diseases, number of prescribers [34, 35], Charlson's

comorbidity score [36], functional status of the patients, length of hospital stay [37-39], educational background [40], cognitive status of patients, type of prescriber [41], type of setting [42-44], and severity of comorbidities [45]. There was no association between gender and the occurrence of PIM, as demonstrated by two studies [43, 46]. Conversely, PIM was significantly associated with the male in a study [47] and several other observational studies found a positive association with the female [35, 42, 44, 45, 48-51]. Likewise inconsistent results have been reported by different studies for age. PIM had no association with age in two studies [43, 52]. However, it was positively associated with younger age in some studies [40, 51, 53-55]. Quite the opposite, some studies found a positive trend of PIM with older age [36, 37, 39, 47, 49, 56-58]. Polypharmacy is often described as a prescription of five or more medications. The polypharmacy in times of multiple disease states may be rational. However, it is full of risk and concomitant use of medications may lead to a complex drug regimen. This further leads to an increased likelihood of medication noncompliance, especially in those with challenged cognitive status [59]. Results from the previous studies have identified polypharmacy [36-39, 42, 43, 45, 47, 50, 51, 53, 56, 60-69] and number of medications [32, 34, 35, 37, 44, 46, 48, 49, 54, 55, 58, 65, 70-79] as the independent predictor of PIM, irrespective of the country, setting, and measurement tool used. Other challenges with polypharmacy are the increased risk of drug-drug, drug-disease and drug-food interactions. Several studies have demonstrated an increasing trend of polypharmacy since the past [80, 81]. Higher disease burden has been linked with a greater likelihood of PIM by several studies [35, 36, 43, 48, 49, 54, 64, 68, 82], except an Israeli study using Beers 2003 criteria [46]. The same study reported no significant relation of PIM with the cognitive and functional status of the elderly [46]. This contrasts with two studies [38, 40] and a systematic review [27] which concluded and increased likelihood of PIM with poor functional status. Likewise, a study conducted in primary care patients using Beers 2015 criteria found a significant association of PIM with cognition [53].

Health-related outcomes

PIM may lead to a decline in several health-related outcomes as evident from several observational studies. The results, however, are inconsistent between the studies. PIM can significantly increase health care costs [83-86]. Despite a systematic review reported an inconclusive association of PIM on length of hospital stay [86], two observational studies have reported elevated duration of hospital stay in patients having PIM [84, 87]. Similarly, mixed results for association [44, 54, 70, 88-92] and no-association [46, 86, 87, 93-98] of PIM with hospital readmissions are present. From the result of a meta-analysis based on Beers and STOPP criteria, it was demonstrated that the PIM based on Beers criteria significantly led to functional decline in the elderly [91]. This finding was consistent with findings from an Italian study [99]. Conversely, some European and American studies deduced that PIM based on Beers criteria is insensitive to characterize functional status and health-related quality of life [100-103]. The PIM may not be significantly associated with mortality as evidenced from several studies [46, 51, 60, 79,

88, 89, 95, 97, 98, 104, 105] including a meta-analyses [91, 106]. A systematic review of studies from 21 different countries found that 8.7% of hospitalization was related to adverse reactions [107]. Different criteria had been found to have different strengths to predict the incidence of adverse reactions. Beers criteria did not significantly predict the adverse events [98, 100, 101], however, results from STOPP criteria [91, 100, 101, 108, 109] and PRISCUS [110] have produced the promising result.

Interventions to prevent inappropriate prescribing

Several interventions have been studied to decrease PIM in elderly patients. Some of the practical interventions include: recruiting clinical pharmacists for treatment optimization, educational interventions for prescribers, peer feedback, multidisciplinary decision-making methods, computer physician order entry (CPOE), clinical decision support system (CDSS), case conferences, and combination of these. Trained and experienced clinical pharmacists can add valuable input during drug utilization review and hence improving the overall prescription quality. For this purpose, the clinical pharmacists must have adequate access to the patient data and have the opportunity to actively cooperate with prescribers. A multidisciplinary team involving experts from different specialties may add specific competencies during drug utilization reviews complimenting each other's incompetencies. Prescribers should be continuously educated and updated about the recent evidence. It can be achieved through active, passive, or a combination of both methods. Continuous education can ultimately alter the prescribing behavior of physicians. However, many times physician education is focused on specific diseases or drugs which may not help to change in overall appropriateness. CPOE and CDSS are very powerful tools that can assist in prescribing medications. These software based approaches can detect all categories of inappropriate prescribing which include drug interactions, wrong dosages, contraindications, and wrong drug choices. Although significant improvements in the prescription quality with the interventions have been observed, there are mixed results for benefit in health-related outcomes such as mortality, adverse drug events, number of hospitalizations, and hospitalization costs [9, 111].

Approaches to improving prescription quality

A step-by-step systematic approach to improving prescribing behavior in the treatment of elderly patients has been proposed, which includes: reviewing current medications; stopping unnecessary treatments; considering new symptoms as a result of adverse events unless proven otherwise; considering nonpharmacological approaches; careful use of common medicines; reducing doses; simplifying dosage and regimen; and prescribing beneficial therapies. The key to appropriate prescribing is the timely review of the therapy so that any errors can be found in time and then make the best changes accordingly. Such changes may include termination of treatment, replacement with a better drug in regards to efficacy and safety, initiation of new drugs, and alteration in dose, dosage form or frequency. Changes in the patient's physiological status must also be considered when reviewing

therapy ^[112].

Drugs that are no longer beneficial and may cause harm can be discontinued or dose adjusted under proper supervision. The process is called deprescribing. For certain drug classes such as proton pump inhibitors (PPI), hypoglycemic agents, antipsychotics, benzodiazepine receptor agonists (BZRA) and cholinesterase inhibitors (CHEIs) and memantine, deprescribing guidelines and algorithms have been proposed. Common to deprescribing algorithms for all the above drug categories is that they recommend shared decision making with patients or caregivers. Patients who are taking PPI for more than four weeks may initiate deprescribing. However, this does not imply to patients having Barret's esophagus, severe esophagitis (Grade C or D), patients with a history of gastrointestinal ulcer bleeding, and patients taking NSAIDs and have a high risk of bleeding ^[113]. While deprescribing for antihyperglycemic agents, three approaches have been recommended which include: reducing doses or terminating agents if hypoglycemic agents are more likely to cause hypoglycemia (such as sulfonylureas and insulin) or adverse events; switching drug with high hypoglycemia risk to a lower risk drug (eg, gliclazide substituted to glyburide, newer long-acting insulins substituted to mixed insulin or NPH); and reducing doses of renally eliminating drugs in conditions of renal function decline. When considering for deprescribing of antihyperglycemics, other potential factors of hypoglycemia should also be ruled out ^[114]. Elderly patients taking higher doses of antipsychotics or suffering from Parkinson's disease or Lewy body dementia are more likely to suffer from side effects such as metabolic disorders, weight gain, anticholinergic side effects, dizziness, falls and hip fractures, cardiovascular events, urinary tract infections, and even death. Therefore, for those elderly patients who have received antipsychotics for BPSD for more than 3 months, who have received antipsychotics for primary insomnia regardless of the treatment duration, and who have been using antipsychotics for secondary insomnia where the underlying cause has already been resolved, the deprescribing approach could be initiated ^[115]. It is recommended that BZRAs should be avoided for treating primary insomnia and secondary insomnia where the underlying cause has already been managed. For these patients, behavioral management should be considered as first-line treatment ^[115].

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