Inappropriate medication use and association with polypharmacy in surgical patients: A retrospective, population-based cohort study

Short running title: Inappropriate medicines and polypharmacy

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Data availability: Data is not publicly available as this was not allowed by our ethical approval.

Background: This study assessed the prevalence and incidence of potentially inappropriate medication use for older patients undergoing surgery and its association with polypharmacy.

Methods: A retrospective, population-based cohort study with patients ≥65 undergoing first surgery at Landspitali – The National University Hospital of Iceland from 2005-2018. Participants were categorized by number of medications filled prior to and following their surgical episode into:non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). The prevalence and incidence of PIM use were compared between polypharmacy categories based on the 2019 Beers criteria.

Results: A total of 17 198 admissions associated with surgery were assessed (53.8% female) with a median [IQR] age of 75 [70,81]. The prevalence of potentially inappropriate medication among patients with non-polypharmacy (<5) was 36.6% (95% CI 35.1-38.2), with polypharmacy (5-9) 80.2% (95% CI 79.2-81.2), and with hyper-polypharmacy 95.8% (95% CI 95.3-96.2). New potentially inappropriate medication use post-surgery occurred in 38.5% (95% CI 37.0-40.1). Risk factors included female sex, increased comorbidity, and prior use of a multidose dispensing service. Compared with patients without potentially inappropriate medication use, patients with potentially inappropriate medication use they had a higher rate of postoperative diagnosis of medication-related harm (12.6% vs. 11.3%), increased 30-day mortality (5.2% vs. 0.3%), longer hospital stay (3 [1,8] vs. 2 [1,5] days), and increased 30-day readmission rate (11.3% vs. 6.5%).

Conclusions: Potentially inappropriate medication use is strongly associated with polypharmacy/hyper-polypharmacy and adverse outcomes in older surgical patients. Surgical hospitalization offers a critical window for medication review, deprescribing, and follow-up planning to reduce medication-related harm.

Word count: 247

Introduction

Significant advances in surgical and perioperative care have enabled surgical treatment for older and patients with a high comorbidity. Polypharmacy is commonly defined as the use of five or more medications[1] and hyper-polypharmacy as the use of ten or more medications.[2] Potentially inappropriate medication (PIM) use occurs when the harm outweighs the benefits of the medication.[3] Polypharmacy and hyper-polypharmacy have been identified as leading risk factors for PIM use.[3-5] The World Health Organization launched a global health campaign highlighting the importance of optimizing medication use among individuals with polypharmacy to reduce medication-related harm.[6] The utilization of multidose drug dispensing (MDD) services, wherein patients receive their medications pre-packaged into unit-dose bags aims enhancing medication adherence and safety, particularly among older adults and those with complex medication regimens, emerging evidence suggests a correlation between MDD and increased instances of polypharmacy[7, 8] and potentially PIM use.[9]

Polypharmacy can be rational in patients with multimorbidity. However, it has also been identified as a potential quality indicator of prescribing practices and a proxy for inappropriate prescribing practices.[4] This underscores the need to evaluate medication appropriateness in patients with polypharmacy to ensure optimal treatment. Furthermore, hospitalization has been associated with the incidence of new polypharmacy and PIM use. [7, 8, 10]

There are several studies on polypharmacy and PIM use among older patients that have focused on general practice[21] and patients admitted to internal medicine[8] , but less is know about the older surgical population.

The study aimed to estimate the prevalence and incidence of PIM use and its association with the burden of polypharmacy among older surgical patients aged >65 years. Furthermore, we examined PIM use in relation to patient characteristics, procedural variables, and medication classes. We hypothesized that PIM use, both pre-admission and post-admission for surgery, would be common,

particularly among those with a high burden of comorbidity and frailty. Additionally, we hypothesied that preoperative PIM use would be associated with increased short- and long-term mortality, extended lengths of primary hospitalization, and an increased risk of readmission.

Methods

Study Population

The retrospective population-based cohort study included all patients aged 65 years and older who underwent their first surgical procedure at Landspitali - The National University Hospital of Iceland- during December 2005 to December 2018, with a follow-up for medication refills and survival until March 11, 2021. The hospital provides secondary surgical care for most of Iceland, accounting for 75%, and tertiary surgical services across the entire nation. The databases used for this study were de-identified prior to statistical analysis and comply with the General Data Protection Regulation of the European Union. The research protocol was published on clinicaltrials.gov before analysis (NCT04805151). The study reporting follows the STROBE guidelines for epidemiological observational research studies.[11] Approval for the study protocol was obtained from the National Bioethics Committee of Iceland (VSN-14-139-V1) and the Data Protection Authority of Iceland, with individual consent waived.

Clinical and medication data

For this study, the Icelandic perioperative database was utilized. This database contains clinical information on all surgeries performed at Landspitali, including elective and emergency, and all specialties.[12] The type and anatomical location of surgery is described using the NOMESCO (Nordic Medico-Statistical Committee) (NCSP-IS, version 1.14) surgical classification.[13] Comorbidities were recorded using the International Classification of Diseases, 9th and 10th revisions (ICD-9/10) from both hospital and primary care databases.[14] The overall comorbidity burden was quantified by calculating the van Raven modified Elixhauser comorbidity index and was categorized as (<1), (1-4), (5-8), and

(>8).[15] The Hospital Frailty Risk Score was used to classify frailty risk into three categories: low risk (<5), intermediate risk (5–15), and high risk (>15).[16] The diagnosis of adverse drug reactions was based on the ICE9/10 codes (Y40-59, X40-59 and T36-59). Information on filled medication, coded by the Anatomical Therapeutic Chemical (ATC) system, was retrieved from the National Prescription Medicines Registry of the Directorate of Health database and included medication refills in the year before the year after discharge from hospital.

Exposure Variable Definition

The primary exposure was the degree of polypharmacy, measured by the number of different medications filled in the year preceding surgical admission to the hospital and in the year following hospital discharge. In this study, classifications were made for non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). Additionally, the prevalence of various medication class usage was calculated using anatomical/pharmacological groups (ATC 1st level) and pharmacological/therapeutical subgroups (ATC 2nd level).

Outcome Data

The primary outcome was the prevalence and incidence of PIM use, assessed using the 2019 Beers criteria.[17] The evaluation was conducted by assessing all prescription medications filled and comparing them against the Beers criteria, which constitutes a list of medications deemed potentially inappropriate for most older adults ≥65 that should typically be avoided. Additionally, the incidence of new PIM use post-admission for surgery was calculated for patients who had not filled a PIM prior to admission. Other clinical outcomes evaluated included short-term (< 30 days) and long-term mortality, length of stay, and the risk of readmission within 30 days, as well as the odds of receiving a diagnosis of an adverse drug reaction post-operative. The likelihood of developing medication-related harm post-admission was assessed by applying the PRIME tool, which predicts the risk of medication-related harm in older adults (≥65) after hospital discharge using clinical, medication, and psychosocial factors.[18, 19]

Statistical analysis

Analysis of the data was performed from January 2023 to April 2025 using R (The R Foundation for Statistical Computing, Austria) version 4.0.3, via Rstudio (RStudio PBC, USA), version 1.4.1106. Descriptive statistics were utilized to summarize the cohort's demographics and clinical characteristics, types of surgical procedures, and clinical outcomes, along with the number of medications filled, which were categorized into non-polypharmacy, polypharmacy, and hyper-polypharmacy. In addition, the prevalence and incidence of PIM use were evaluated based on the 2019 Beers criteria. The proportion of patients receiving PIM use was reported with a 95% confidence interval by calculating using the Pearson-Klopper method in the binom package in R.

A restricted cubic spline model was employed to illustrate the association between the number of medications filled and the proportion of patients filling a PIM. Knots were prespecified at 0, 5, and 10 medications.

A multivariable logistic regression model was generated to identify the patient- and procedure-related risk factors associated with the initiation of a new prescription for a PIM. Covariates included age, sex (female versus male), Elixhauser comorbidity index (≥1 versus <1), MDD service (versus non-use), pre-admission medication use category (polypharmacy and hyper-polypharmacy versus non-polypharmacy), and documented diagnosis of fall or adverse drug reaction diagnosis prior to admission, as covariates. No missing data were identified; however, it is noted that the absence of a record of a condition (diagnosis or medication) is interpreted as the condition not being present.

Results

The study cohort included 30 082 surgical patients 65 years and older. Of these, 12 884 (42.8%) had non-first surgeries during the study period, which included reoperations or subsequent unrelated surgeries. Excluding these secondary surgeries, the final study population consisted of 17 198 patients who underwent their first surgery within the study period. (Figure 1) Out of the entire cohort, 9252

(53.8%) were female, and the median age of all patients [IQR] was 75 [70, 81]. Most of the study cohort had a low (<5) hospital frailty risk score class 12276 (71.4%). the most common comorbidities were hypertension (57.0%), ischemic heart disease (32.1%) and malignant neoplasm (27.7%). The most common surgical procedures were orthopedic (37.5%), abdominal (14.4%), and urological (11.4%), with the majority being elective (67.3%). They used a median [IQR] of 9 [5,13] medications in the year preceding the admission and 9 [6,14] post-admission for surgery and MDD service was utilized by 32.8% of the cohort.

Out of all patients included in the study cohort 13 386 (77.8%), 95% (CI 77.2-78.5%) filled a prescription for at least one PIM use in the year preceding the admission (Table 1). Figure 1 illustrates the prevalence of PIM across various levels of pre-admission polypharmacy. Among patients with non-polypharmacy, the prevalence of PIM use was 36.6% (95% CI 35.1-38.2), compared to 80.2% (95% CI 79.2-81.2) for those with polypharmacy and 95.8% (95% CI 95.3-96.2) for patients with hyper-polypharmacy, respectively.

Table 1 presents the characteristics of the patients, their comorbidities, the surgical procedures performed, and the clinical outcomes compared between patients who did and did not fill a PIM prior to admisson. Patients with PIM use were more likely to be female (57.0% vs. 42.5%) and to fill more medications both prior to and following admission. MDD service was used more frequently by those who had filled a PIM, 36.0% compared to 21.3%. They also had a higher burden of comorbidities quantified with Elixhauser comorbidity Index 2 [0,5] vs. 0 [0,4] and a higher Hospital Frailty Risk score class with 30.2% vs 23.3% having medium or high-risk score class.

Table 1 additionally compares the urgency and surgical classification of the patients. Patients with PIM use were less likely to undergo emergency surgery (30.0% vs. 42.1%). Patients with PIM use were more likely to undergo the following surgeries abdominal surgery (14.9% vs. 12.8%), neurosurgery (9.3% vs. 5.5%) and gynecology (6.4% vs. 2.6%). Additionally, they were more likely to have a higher PRIME risk

estimate of the risk of experiencing medication-related harm post-admission, with a median [IQR] of 10.7 [7.2-14.5] compared to 10.2 [7.4-15.3].

Incidence of new PIM use

Table 2 compares patient characteristics, types of surgery, comorbidities, and clinical outcomes between cohorts of patients prescribed a new PIM following discharge (1481, 38.5%, 95% CI 37.0-40.1) and those who continued without filling a PIM (2366, 61.5%, 95% CI 59.9-63.0). Patients prescribed new PIM were more likely to be female (60.0% vs. 56.5%), utilize MDD services (28.4% vs. 17.1%), and take a higher number of medications both prior to admission (5[2,7] vs. 3[0,6]) and post-discharge for surgery (9 [6,12] vs. 3 [0,6]). Additionally, they had a higher Elixhauser risk score (4 [0,7] vs. 2 [0,6]) but a lower Hospital frailty risk score classification (75.4% vs. 78.4% having a low-risk classification). Patients prescribed a new PIM were more likely to have malignant neoplasm (29.2% vs. 19.4%), ischemic heart disease (29.6% vs. 20.3%), and hypertension (18.5% vs. 15.4%), and less likely to have a diagnosis of a psychiatric condition (6.2% vs. 11.4%), dementia (1.8% vs. 4.4%), and delirium (2.6% vs. 3.9%). Patients prescribed a new PIM post-admission for surgery were more likely to undergo cardiac surgery (14.9% vs. 4.4%), vascular surgery (11.1% vs. 8.2%), and gynecological surgery (4.3% vs. 1.7%) and less likely to undergo orthopedic surgery (28.6% vs. 47.0%) and emergency surgery (31.9% vs 48.3%).

Patients prescribed a new, PIM post-admission for surgery were more likely to have a longer hospital stay (3 [1,8] vs. 2 [1,5] days), a higher 30-day readmission risk (11.3% vs. 6.5%), and increased 30-day mortality (5.2% vs. 0.3%). Additionally, patients with new, PIM were more likely to receive a diagnosis of an adverse drug reaction both prior to hospital admission (3.7% vs. 3.3%) and post-admission for surgery (3.7% vs. 2.2%).

Figure 2 shows the results of a multivariable logistic regression model applied to evaluate patient- and admission-related variables associated with a new prescription for a PIM in the year following discharge. After adjustment for comorbidities and admission information, filling a prescription for a

new PIM use following discharge was associated with higher odds of using pre-admission MDD service (OR 2.52, 95% CI 2.11-3.02), pre-admission hyper-polypharmacy (OR 2.40,95% C 1.3.10), pre-admission polypharmacy (OR 1.76,95% CI 1.51-2.05) and pre-admission malignant neoplasm (OR 1.83, 95% CI 1.55-2.16). However, having a diagnosis of pre-admission dementia was associated with lower odds (OR 0.47, 95% CI 0.29-0.73) of filling a prescription for PIM. Figure 3 illustrates an unadjusted restricted cubic spline analysis demonstrating a non-linear association between the absolute number of different medications filled in the year preceding admission and the rate of PIM use. The highest proportion of patients filled prescriptions for PIMs acting on the central nervous system and gastrointestinal system. Further analysis of these categories revealed a strong relationship between increasing levels of pre-admission polypharmacy and the likelihood of having filled a prescription for benzodiazepines and Z-drugs (Figure 4), as well as for gastrointestinal medications that act on the gastrointestinal system, particularly proton pump inhibitors (Figure 5).

Supplementary table 1 compares the Beers criteria subgroups met by the entire cohort, categorized by varying degrees of polypharmacy prior to admission. The most frequently observed Beers criteria among the entire cohort in the year prior to admission were for medications that act on the central nervous system (50.0%), with z-drugs being the most common (36.2%), followed by benzodiazepines (22.7%). The second most frequently encountered Beers criteria were gastrointestinal medications (35.2%), with proton pump inhibitors being the most common (34.0%). The most frequently added medication post-admission for surgery that met Beers criteria were proton pump inhibitors (11.3%), Z-drugs (9.7%), benzodiazepines (6.4%), antipsychotics (3.3%) and anticholinergics (3.8%).

Discussion

This study identifis that pre-admission PIM use among older surgical patients is common and increases with the rising burden of polypharmacy. Additionally, the use of new, PIM post-admission was high among the surgical cohort. The findings confirm that pre-admission use of PIM is associated with higher short-term mortality, longer primary hospital stays, and a higher 30-day readmission rate.

Previous studies have examined PIM use, revealing that its prevalence and incidence vary among countries; however, there is a general trend of increasing prevalence of PIM use.[1, 20-25] These studies are often difficult to compare due to methodological differences and heterogeneous study populations.

PIM use can be evaluated through various criteria.[26] Beers criteria have been widely studied in general practice [3, 27] and hospital settings[28], but few studies have focused solely on surgical patients. This study found that the prevalence of pre-admission filling of a PIM was 77.8%, which is lower than the 82.7% reported in our recently published study utilizing the same methodology in patients admitted by internal medicine.[8] The reported prevalence of PIM use varies across different settings. A meta-analysis examined the prevalence in outpatient settings, revealing a range from 1.3% to 95.2%, with a pooled prevalence of 36.7%. [29] However, a recently published study on older internal medicine patients reveals the vast difference between patients admitted to internal medicine and those admitted to surgical wards.[28] Generally, internal medicine patients are older, have higher comorbidities and increased frailty, and use more medications than surgical patients; therefore, they are also more likely to use PIMs.[8] These results also emphasize the need for tailored care for surgical patients. They may benefit from targeted interventions to optimize medication therapy prior to elective surgery, with an emphasis on reducing the use of PIMs, especially those known to impact clinical outcomes related to surgery, such as benzodiazepines and opioids. [12] For patients with a high burden of comorbidities and associated polypharmacy or hyperpolypharmacy, geriatricians and clinical pharmacists could offer specialized perioperative care. [30-32] Furthermore, there should be a greater emphasis on enhancing follow-up for new medications introduced during surgical admissions to empower patients and their caregivers to mitigate the risk of their use by providing adequate information and guidance on temporary use and support. Although the surgical population is generally younger and has fewer comorbidities, there are also complex surgical patients who might benefit from a multidisciplinary perioperative approach involving internal medicine specialists, geriatricians, and

clinical pharmacists, which would provide a comprehensive review and increased follow-up during transitions of care.

Another option is to utilize risk stratification tools like PRIME tool to identify patients at risk of experiencing medication-related harm after discharge.[19] One potential application could be using it as risk stratification post-discharge to guide support by categorizing patients into appropriate follow-up levels. For example, low-risk patients could receive assistance from a community pharmacy, moderate-risk patients from clinical pharmacists prescribers or doctors within general practice and high-risk patients from a specialist pharmacist or geriatrician in outpatient settings.

The results of this study indicate a correlation between female sex and PIM use (57.0% vs. 43.0%), which aligns with previous research studies.[3, 33, 34] Studies have identified that females are more likely to have polypharmacy and hyperpolypharmacy, which is associated with an increased risk of PIM use.[7, 28, 35] These findings may be explained by the fact that females are more often prescribed medications that act on the central nervous system, such as benzodiazepines and Z-drugs[33] . They are also more likely to visit healthcare providers more frequently, which may create additional opportunities for new prescriptions. [36] This warrants further research into the gender differences in the use of potentially inappropriate medications. The findings from this study should highlight the necessity for healthcare practitioners to recognize sex and gender differences concerning the use of PIM. There are significant differences between genders regarding biological factors that influence the pharmacokinetics and pharmacodynamics of medications.[37-39] This study found an association between the use of MDD services and PIM use, which aligns with previous research.[9] These findings highlight the importance of systematically reviewing medications dispensed via MDD services. Prior studies have identified MDD as a risk factor for uncritical prescription renewals and suboptimal medication optimization. [23, 40, 41] The use of MDD services was associated with a higher likelihood of developing new, PIM use after discharge. This may be due to patients who utilize MDD services generally being older and exhibiting greater comorbidity and more complex healthcare needs. Due to the heavy workload in primary care,

primary care physicians often find it challenging to provide these review services.[42] Clinical pharmacists may be able to support providing the service, helping to alleviate the burden on physicians and ensure patients receive comprehensive medication reviews.

In line with the previously stated hypothesis, this study found that PIM use is linked to worse clinical outcomes, such as extended hospital stays, increased readmission risk, mortality, and a higher likelihood of adverse drug reactions, which is largely in line with previous research. It is unclear whether PIM use directly causes poorer clinical outcomes or whether it serves as a marker of increased comorbidity. However, various studies have reported that PIM use may lead to worse clinical outcomes due to adverse drug events, such as side effects due to increased anticholinergic burden, fall risk, delirium, extended hospital stays, readmission, and increased mortality.[43-46]

It is essential to review the use of new medications after a surgical admission, as they are typically intended for short-term use. Hyperpolypharmacy and polypharmacy are also linked to a higher risk of acquiring new, PIM following surgical admission. Additionally, patients with malignant neoplasms were at increased risk for polypharmacy and PIM with spikes towards the end of life, which are often questionable prescriptions both for symptamatic control but also longterm preventive meidcations.[47] Studies have reported that older patients with malignant neoplasms exhibit greater frailty and geriatric syndromes compared to older adults without malignant neoplasms and are more vulnerable to PIM use, which may also affect cancer therapy negatively. [48] The diagnosis of dementia was linked to lower odds of developing new, PIM use post-admission for surgery, possibly due to healthcare providers' awareness of the increased risk of adverse drug events associated with such medications, including anticholinergic burden and fall risk delirium.

The most frequently prescribed PIMs in the year leading up to a surgical admission were those affecting the central nervous system, such as Z-drugs and benzodiazepines which emphasizes the importance of medication optimization as a part of the pre-operative management. For elective

surgeries, the waiting time for an upcoming surgery provides an ideal opportunity to deliver focused intervention on medicines optimization. After surgical admission, the most frequently used new PIMs included proton pump inhibitors, Z-drugs, and benzodiazepines. These medication categories are generally intended for short-term treatments, which should be evaluated soon after admission. This highlights the importance of clear counselling for patients and caregivers during the transition of care and handover to primary care following discharge as they may cause adverse drug events like delirium[49] and falls.[50]

The study's strengths include a nationwide centralized Prescription Medicine Registry, which provides detailed information covering over 95% of all prescriptions in the country. It also facilitates the linking of various registries and the collection of information through personal identification numbers. Another strength is the large number of participants included in the extensive surgical database and the comprehensive follow-up for survival analysis. Additionally, all surgeries were conducted at the same national hospital.

A limitation worth mentioning is the using medication filling as a proxy for medication use. This approach may inflate the number of medications participants take regularly due to insufficient information on medication adherence. However, there is also an underestimation because over-the-counter medications are not included, as well as medications often used as combination drugs, such as angiotensin receptor blockers combined with a thiazide, which are counted as one medication. Furthermore, we cannot confirm that the increased risk of readmission, mortality, and extended hospitalization is attributable to medication-related problems. Additionally, it should be noted that, because of variations in healthcare systems and prescribing practices across different countries, these results may have limited relevance in other nations.

Conclusion

This study revealed a strong association between the increased burden of PIM use, polypharmacy, and hyper-polypharmacy. Certain sub-groups were at a greater risk of developing increased PIM use after admission, highlighting the need for enhanced follow-up and medication review. Surgical hospitalization presents an opportunity to review and optimize medication regimens. When medications are added or modified during admission, it essential to ensure appropriate follow-up and continuity of care during transitions. Additionally, our study highlights the necessity for improved follow-up for patients at risk of acquiring new PIM after admission. Ideally, this process should include a targeted medication review and deprescribing performed by a multidisciplinary team including to patients at highest risk.

A disclosure statement: The authors declare no conflicts of interest.

Funding: This work was supported by the Foundation of St. Josef's Hospital in cooperation with The Icelandic Gerontological Research Centre, National University Hospital of Iceland, to Freyja Jónsdóttir, Landspitali University Hospital Science Fund, to Martin Ingi Sigurðsson, and the University of Iceland Research Fund to Freyja Jónsdóttir.

Author Contributions

F.J., A.B.B., A.G., I.B., J.M.S. and M.I.S. contributed to the study's conceptualisation, methodology, and validation. F.J. and M.I.S. were responsible for data curation, formal analysis, investigation, project administration, and funding acquisition. M.I.S. provided resources and supervision. F.J., A.B.B., A.G., I.B., J.M.S. and M.I.S. contributed to visualisation. All authors analysed and interpreted the data, commented on, revised, and approved the final version of the manuscript.

References

1. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. Therapeutic advances in drug safety. 2020;11:2042098620933741.
2. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. Clinical pharmacology and therapeutics. 2012;91(3):521-8.
3. Al-Azayzih A, Alamoori R, Altawalbeh SM. Potentially inappropriate medications prescribing according to Beers criteria among elderly outpatients in Jordan: a cross sectional study. Pharmacy practice. 2019;17(2):1439.
4. Burt J, Elmore N, Campbell SM, Rodgers S, Avery AJ, Payne RA. Developing a measure of polypharmacy appropriateness in primary care: systematic review and expert consensus study. BMC medicine. 2018;16(1):91.
5. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. 2015;5(9):e008656.
6. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny MP, Sheikh A. Medication Without Harm: WHO's Third Global Patient Safety Challenge. Lancet (London, England). 2017;389(10080):1680-1.
7. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Epidemiology and association with outcomes of polypharmacy in patients undergoing surgery: retrospective, population-based cohort study. BJS Open. 2023;7(3).
8. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Potentially inappropriate medication use before and after admission to internal medicine for older patients and polypharmacy. Am J Med. 2024.
9. Johnell K, Fastbom J. Multi-dose drug dispensing and inappropriate drug use: A nationwide register-based study of over 700,000 elderly. Scandinavian journal of primary health care. 2008;26(2):86-91.
10. Weiss O, Eyre A, Ellenbogen DA, Stein GY. The impact of hospitalization on inappropriate prescribing and polypharmacy in older patients: A descriptive cross-sectional study. Pharmacoepidemiology and drug safety. 2024;33(5):e5812.
11. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JPJBotWHO. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. 2007;85:867-72.
12. Sigurdsson MI, Helgadottir S, Long TE, Helgason D, Waldron NH, Palsson R, et al. Association Between Preoperative Opioid and Benzodiazepine Prescription Patterns and Mortality After Noncardiac Surgery. JAMA surgery. 2019;154(8):e191652.
13. Statistics NgoM. 2024 [cited 2024 21.05]. Available from: https://nhwstat.org/health/pharmaceutical-products/sales/consumption-opioids-nordic-countries-and-development-during.
14. NOMESCO N. NOMESCO Classification of Surgical Procedures (NCSP), version 1.14. 2009.
15. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Medical care. 1998;36(1):8-27.
16. Gunnarsdottir GM, Helgadottir S, Einarsson SG, Hreinsson K, Whittle J, Karason S, et al. Validation of the Hospital Frailty Risk Score in older surgical patients: A population-based retrospective cohort study. Acta anaesthesiologica Scandinavica. 2021;65(8):1033-42.
17. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2019;67(4):674-94.

18. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of Medication-Related Harm in Older Adults After Hospital Discharge: A Systematic Review. Journal of the American Geriatrics Society. 2018;66(9):1812-22.
19. Stevenson J, Parekh N, Ali K, Timeyin J, Bremner S, Van Der Cammen T, et al. Protocol for a Prospective (P) study to develop a model to stratify the risk (RI) of medication (M) related harm in hospitalized elderly (E) patients in the UK (The PRIME study). BMC geriatrics. 2016;16:22.
20. Castioni J, Marques-Vidal P, Abolhassani N, Vollenweider P, Waeber G. Prevalence and determinants of polypharmacy in Switzerland: data from the CoLaus study. BMC health services research. 2017;17(1):840.
21. Franchi C, Marcucci M, Mannucci PM, Tettamanti M, Pasina L, Fortino I, et al. Changes in clinical outcomes for community-dwelling older people exposed to incident chronic polypharmacy: a comparison between 2001 and 2009. Pharmacoepidemiology and drug safety. 2016;25(2):204-11.
22. Jørring Pallesen AV, Kristiansen M, Westendorp RGJ, Mortensen LH. Polypharmacy occurrence and the related risk of premature death among older adults in Denmark: A nationwide register-based cohort study. PloS one. 2022;17(2):e0264332.
23. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clinical epidemiology. 2018;10:289-98.
24. Rachamin Y, Jäger L, Meier R, Grischott T, Senn O, Burgstaller JM, et al. Prescription Rates, Polypharmacy and Prescriber Variability in Swiss General Practice-A Cross-Sectional Database Study. Frontiers in pharmacology. 2022;13:832994.
25. Sganga F, Landi F, Ruggiero C, Corsonello A, Vetrano DL, Lattanzio F, et al. Polypharmacy and health outcomes among older adults discharged from hospital: results from the CRIME study. Geriatrics & gerontology international. 2015;15(2):141-6.
26. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. European journal of clinical pharmacology. 2014;70(1):1-11.
27. Guaraldo L, Cano FG, Damasceno GS, Rozenfeld S. Inappropriate medication use among the elderly: a systematic review of administrative databases. BMC geriatrics. 2011;11:79.
28. Jónsdóttir F, Blöndal AB, Guðmundsson A, Bates I, Stevenson JM, Sigurðsson MI. Potentially inappropriate medication use before and after admission to internal medicine for older patients and polypharmacy. The American Journal of Medicine. 2024.
29. Tian F, Chen Z, Zeng Y, Feng Q, Chen X. Prevalence of Use of Potentially Inappropriate Medications Among Older Adults Worldwide: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2023;6(8):e2326910.
30. Shahab R, Lochrie N, Moppett IK, Dasgupta P, Partridge JSL, Dhesi JK. A Description of Interventions Prompted by Preoperative Comprehensive Geriatric Assessment and Optimization in Older Elective Noncardiac Surgical Patients. Journal of the American Medical Directors Association. 2022;23(12):1948-54.e4.
31. Care CfP. Perioperative Care of People Living with Frailty 2021 [Available from: https://cpoc.org.uk/guidelines-and-resources/guidelines/perioperative-care-people-living-frailty.
32. Partridge JSL, Ryan J, Dhesi JK. New guidelines for the perioperative care of people living with frailty undergoing elective and emergency surgery-a commentary. Age and ageing. 2022;51(11).
33. Alwhaibi M, Balkhi B. Gender Differences in Potentially Inappropriate Medication Use among Older Adults. Pharmaceuticals (Basel). 2023;16(6).
34. Doheny M, Schön P, Orsini N, Fastbom J, Burström B, Agerholm J. Socio-demographic differences in polypharmacy and potentially inappropriate drug use among older people with different care needs and in care settings in Stockholm, Sweden. Scandinavian Journal of Public Health. 2023;51(1):11-20.
35. Jonsdottir F, Blondal AB, Gudmundsson A, Bates I, Stevenson JM, Sigurdsson MI. The association of degree of polypharmacy before and after among hospitalised internal medicine

patients and clinical outcomes: a retrospective, population-based cohort study. BMJ open. 2024;14(3):e078890.
36. National Academies of Sciences E, Medicine, Health, Medicine D, Board on Health Care S, Committee on Health Care U, et al. Health-Care Utilization as a Proxy in Disability Determination. Washington (DC): National Academies Press (US)

37. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biology of sex differences. 2020;11:1-14.
38. Franconi F, Campesi I. Sex and gender influences on pharmacological response: an overview. Expert review of clinical pharmacology. 2014;7(4):469-85.
39. O'Mahony D, Cruz-Jentoft AJ, Gudmundsson A, Soiza RL, Petrovic M, Cherubini A, et al. Sex differences in patterns of potentially inappropriate prescribing and adverse drug reactions in hospitalized older people: Findings from the SENATOR trial. Journal of the American Geriatrics Society. 2024;72(11):3476-83.
40. Tang J, Wang K, Yang K, Jiang D, Fang X, Su S, et al. A combination of Beers and STOPP criteria better detects potentially inappropriate medications use among older hospitalized patients with chronic diseases and polypharmacy: a multicenter cross-sectional study. BMC geriatrics. 2023;23(1):44.
41. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, et al. Effect of Reminder Devices on Medication Adherence: The REMIND Randomized Clinical Trial. JAMA Intern Med. 2017;177(5):624-31.
42. Mair A, Wilson M, Dreischulte T. The polypharmacy programme in Scotland: realistic prescribing. Prescriber. 2019;30(8):10-6.
43. Hedna K, Hakkarainen KM, Gyllensten H, Jönsson AK, Petzold M, Hägg S. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. European journal of clinical pharmacology. 2015;71(12):1525-33.
44. Muhlack DC, Hoppe LK, Weberpals J, Brenner H, Schöttker B. The Association of Potentially Inappropriate Medication at Older Age With Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies. Journal of the American Medical Directors Association. 2017;18(3):211-20.
45. Nordin Olsson I, Runnamo R, Engfeldt P. Medication quality and quality of life in the elderly, a cohort study. Health and quality of life outcomes. 2011;9:1-9.
46. Wallace E, McDowell R, Bennett K, Fahey T, Smith SM. Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. The Journals of Gerontology: Series A. 2016;72(2):271-7.
47. Morin L, Vetrano DL, Rizzuto D, Calderón-Larrañaga A, Fastbom J, Johnell K. Choosing Wisely? Measuring the Burden of Medications in Older Adults near the End of Life: Nationwide, Longitudinal Cohort Study. Am J Med. 2017;130(8):927-36.e9.
48. Jørgensen TL, Herrstedt J. The influence of polypharmacy, potentially inappropriate medications, and drug interactions on treatment completion and prognosis in older patients with ovarian cancer. J Geriatr Oncol. 2020;11(4):593-602.
49. Edinoff AN, Nix CA, Hollier J, Sagrera CE, Delacroix BM, Abubakar T, et al. Benzodiazepines: Uses, Dangers, and Clinical Considerations. Neurol Int. 2021;13(4):594-607.
50. Seppala LJ, Petrovic M, Ryg J, Bahat G, Topinkova E, Szczerbińska K, et al. STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk): a Delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age and ageing. 2020;50(4):1189-99.

Figure Legends

Figure 1.

A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding surgical admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy), and the proportion of participants within each group filling at least one potentially inappropriate medications based on 2019 Beers criteria.

Figure 2.

The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), Elixhauser comorbidity index class (compared with <1), individual comorbidities, use of multidose dispensing service (compared with no use), category of medication usage (polypharmacy and hyper-polypharmacy compared with non-polypharmacy) prior to admission and a diagnosis of an adverse drug reaction diagnosis prior to a surgical admission, as covariates.

Figure 3.

The correlation between the number of different medications filled (x-axis) pre-admission and the ratio (y-axis) of patients who filled a prescription within a subcategory of medication that is potentially inappropriate based on the 2019 Beers criteria. The figure shows the result of the restricted cubic spline analysis of the proportion of patients with the different polypharmacy categories. Colors indicate the polypharmacy category based on the different medications filled in the year preceding surgical admission (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy).

Figure 4.

The association between the number of medications pre-admission and risk of potentially inappropriate medication use based on the 2019 Beers criteria for specific medications acting on the central nervous system. The figure shows the result of the restricted cubic spline analysis of the proportion of patients with the different polypharmacy categories. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission.

Figure 5.

The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for medications acting on gastrointestinal system. The figure shows the result of the restricted cubic spline analysis of the proportion of patients with the different polypharmacy categories. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding surgical admission.