Potentially inappropriate medication use before and after admission to internal medicine for older patients and polypharmacy

Freyja Jónsdóttir Cand.Pharm, MS ,
Anna B. Blöndal Cand.Pharm, Ph.D ,
Aðalsteinn Guðmundsson MD , Ian Bates MPharm, Ph.D. ,
Jennifer M. Stevenson MPharm, Ph.D. ,
Martin I. Sigurðsson MD, Ph.D

PII: S0002-9343(24)00475-3
DOI: https://doi.org/10.1016/j.amjmed.2024.07.026
Reference: AJM 17653

To appear in: *The American Journal of Medicine*

Received date: 31 March 2024
Accepted date: 15 July 2024

Please cite this article as: Freyja Jónsdóttir Cand.Pharm, MS , Anna B. Blöndal Cand.Pharm, Ph.D , Aðalsteinn Guðmundsson MD , Ian Bates MPharm, Ph.D. , Jennifer M. Stevenson MPharm, Ph.D. , Martin I. Sigurðsson MD, Ph.D , Potentially inappropriate medication use before and after admission to internal medicine for older patients and polypharmacy, *The American Journal of Medicine* (2024), doi: https://doi.org/10.1016/j.amjmed.2024.07.026

Potentially inappropriate medication use before and after admission to internal medicine for older patients and polypharmacy

Short running title: Inappropriate medication use and polypharmacy

Freyja Jónsdóttir Cand.Pharm MSa,b, Anna B. Blöndal Cand.Pharm Ph.Da,c, Aðalsteinn Guðmundsson MDd,e, Ian Bates MPharm. Ph.D. f, Jennifer M. Stevenson MPharm Ph.D. g ,h, Martin I. Sigurðsson MD Ph.D,i

a Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

b Pharmacy Services, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland

c Development Centre for Primary Healthcare in Iceland, Reykjavik, Iceland

d Division of Geriatrics, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland

e Faculty of Medicine, University of Iceland, Reykjavik, Iceland

f School of Pharmacy, University College London, United Kingdom

g Institute of Pharmaceutical Science, King's College, London, United Kingdom

h Pharmacy Department, Guys and St Thomas' NHS Foundation Trust, London, United Kingdom

i Division of Anaesthesia and Intensive Care Medicine, Landspitali -The National University Hospital of Iceland, Reykjavik, Iceland

Corresponding Author: Freyja Jónsdóttir, Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland. Email: freyjaj@hi.is. Tel: +354-6952240

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 by the allocation of a grant to Freyja Jónsdóttir, Landspitali University Hospital Science Fund providing a grant to Martin Ingi Sigurðsson and the University of Iceland Research Fund´s grant to Freyja Jónsdóttir.

Declaration of interest: None.

Abstract word count: 247

Manuscript word count: 2775

References: 24

Keywords: Polypharmacy, hyper-polypharmacy, potentially inappropriate medication, medication-related problems, aged.

Background: With the aging of the population and the increase in chronic diseases, there is an inherent risk of polypharmacy and inappropriate medication use. The study aimed to determine the prevalence and incidence of potentially inappropriate medication use and its correlation with polypharmacy.

Methods: A retrospective, population-based cohort study among patients ≥65 years hospitalized at The National University Hospital of Iceland from 2010-2020. Data on medication usage were retrieved from the National Prescription Medicine Registry. Based on the number of medications filled in in the year prior to admission and post-discharge, participants were categorized non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10). The prevalence and incidence of potentially inappropriate medication use was assessed based on the 2019 Beers criteria. Regression models were used to correlate sociodemographic, clinical, and pharmacoepidemiologic variables and the odds of new potentially inappropriate medication use.

Results: The cohort comprised 55,859 patients (48.5% male) with a median [IQR] age of 80 [73-86] years. The prevalence of inappropriate medication use in the year preceding admission was 34.0%, 77.7%, and 96.4% for patients with non-polypharmacy, polypharmacy, and hyper-polypharmacy. The incidence of new potentially inappropriate medication use was 46.7% (95% CI 45.6%-47.6%) among those with no potentially inappropriate medication use pre-admission. Factors associated with higher odds of new potentially inappropriate medication use after discharge were the use of multi-dose dispensing services, dementia, polypharmacy, and hyper-polypharmacy.

Conclusions and Relevance: An increased emphasis is needed to review and reevaluate the appropriateness of medication use among older population in internal medicine.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT05756400

Introduction

Polypharmacy refers to using multiple medicines, most commonly five or more, whereas hyper-polypharmacy has been defined as the utilization of ten or more medications [1,2] It is estimated that multimorbidity, and consequently polypharmacy, will increase significantly in the coming years.[1,3-5]

The ratio of older individuals who fill potentially inappropriate prescriptions has been reported within a wide range of 11.5% to 62.5%.[6] Potentially inappropriate medication use is associated with adverse health and economic outcomes. An assessment of inappropriate medication practices may help to identify which sub-groups of patients may need additional interventions to tackle potentially inappropriate medication use. [7,8]

One of the most used criteria to identify inappropriate medication use is the Beers criteria, which provides a list of potentially inappropriate medications in older adults (≥65 years) which has been linked to an increased risk of developing adverse drug reactions. [9,10]

Patients admitted to internal medicine services generally have a high burden of comorbidity and frailty. Recently, we identified that in this cohort, the prevalence of polypharmacy is high, and given that polypharmacy increases the likelihood of potentially inappropriate medication use, this is likely to be also true in this cohort[11]

The study aimed to determine the prevalence and incidence of potentially inappropriate medication use in older patients admitted to internal medicine services and the correlation with polypharmacy. Furthermore, we studied the new potentially inappropriate medication use following admission and the correlation with internal medicine subspecialties and patient-specific variables. We hypothesized that pre- and post-discharge potentially inappropriate medication use was common among older patients with a high comorbidity and frailty burden. Our hypothesis was additionally that potentially inappropriate medication use pre-admission was correlated with a higher short- and long-term mortality, a longer primary hospitalization length of stay, and a higher risk of readmission.

Methods

Study population

This retrospective population-based cohort study included all patients ≥65 years admitted by internal medicine at Landspitali - The National University Hospital of Iceland between 1 January 2010 and 31 December 2020 and clinical outcomes through 17 March 2022. The National Bioethics Committee of Iceland (VSN-21-179) and the Data Protection Authority of Iceland approved the study, waiving individual consent. All databases used for research were de-identified before statistical analysis, and all work was compliant with the General Data Protection Regulation of the European Union. The study protocol was published on clinicaltrials.gov before analysis (NCT04805151), and the study reporting adheres to the STROBE guideline reporting of observational studies in epidemiology.[12]

Clinical and medication data

We used the Icelandic Internal medicine admission database, which includes clinical and medication data for admissions by internal medicine. Generation of the database has been described previously. [11] . The comorbidity burden was described using the Elixhauser comorbidity index, and the frailty risk estimated by calculating the Hospital Frailty Score.[13] For diagnosis of adverse drug reaction, we classified adverse drug reaction (ICD codes, Y40-59, X40-59, T36-59) based on whether the diagnosis was made pre- or post-admission. Medication information was based on filled medications according to the Prescription Medicines Registry of the Directorate of Health database using the ATC classification. This national electronic database includes real-time information about all regular and as-required prescriptions but excludes those prescribed during hospitalization, over-the-counter, topical, and herbal medications. This study obtained data on filled prescriptions and whether an automated multidose drug dispensing service was used. These services, where tablets and capsules are removed from the original package and machine packed into plastic pouches, are frequently implemented to assist with medication adherence.

Exposure Variable Definition

The primary exposure was polypharmacy, classified by the number of medications filled in the year prior to admission to the hospital and the year following hospital discharge. The medication use categories used in this study were non-polypharmacy (<5), polypharmacy (5-9), and hyper-polypharmacy (≥10).

Outcome Data

The primary outcome was the prevalence of potentially inappropriate medication use on admission assessed by applying the 2019 AGS Beers criteria.[10] All prescription medications filled were assessed for potentially inappropriate medication use by comparing them to the list of medications in the Beers criteria that are potentially inappropriate in most older adults, those that should typically be avoided. [10] The incidence of new potentially inappropriate medication use post-discharge was estimated for those patients without the exposure to potentially inappropriate medication use prior to admission only. Secondary outcomes evaluated were short (30-day) and long-term mortality, long primary hospitalization length of stay (≥ 10 days), and readmission within 30 days.

Statistical analysis

Statistical analyses were performed using R (The R Foundation for Statistical Computing R, Austria) version 4.0.3, via R studio (RStudio PBC, USA), version 1.4.1106. Descriptive statistics were applied to describe the demographics, clinical characteristics and clinical outcomes of the cohort, and polypharmacy and potentially inappropriate medication use based on Beers criteria. The ratio of potentially inappropriate medication use was described using 95% confidence interval by applying the Pearson-Klopper in binom package in R.

A Restricted cubic spline was used to determine the likelihood of potentially inappropriate medication use by a number of prescribed medications, with prespecified knots at 0,5, and 10 medications.

A multivariable logistic regression model was generated to estimate the patient- and admission-related risk factors of receiving a new prescription for a potentially inappropriate medication using age, sex (female compared with male), admitting specialty (compared with general medicine), Elixhauser comorbidity index (compared with <1), comorbidities, 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 fall or adverse drug reaction diagnosis prior to admission, as covariates. The change in the incidence of potentially inappropriate medication use with time was assessed with Poisson regression. There were no missing variables identified although it is noted that the absence of a registration of a condition (diagnosis or medication) is coded as the condition not being present, which is an assumption.

Results

Clinical characteristics of the patient cohort and potentially inappropriate medication use

The study cohort included 55 859 admissions to internal medicine services for patients 65 years and older at Landspitali University Hospital. Of the admissions, 82.7% (95% CI 82.4-83.0) had potentially inappropriate medication use in the year prior to admission, without a change in the prevalence of potentially inappropriate medication use pre-admission over the study period. (Figure S_1) Table 1 compares the patient characteristics, admitting specialty, comorbidity, and clinical outcomes between the patient cohorts based on whether the patients had potentially inappropriate medication use prior to admission or not. Patients with potentially inappropriate medication use burden were more likely to be female (51.7% vs. 48.3%), use more medications (4 [1-7] vs. 13 [9-19]), and use multi-dose dispensing services (59.1% vs. 40.9%). Their burden of comorbidity and frailty and the distribution among internal medicine specialties was similar.

Patients with potentially inappropriate medication use were more likely to have been diagnosed with adverse drug reaction prior to admission (12.3% vs 4.5%) and receiving such diagnoses post-discharge

(6.7% vs 3.2%). There was no statistical difference in the length of stay, 30-day readmission rate, and 30-day mortality rate between the groups.

Incidence of new potentially inappropriate medication use

Table 2 compares the patient characteristics, admitting specialty, comorbidity, and clinical outcomes between cohorts, between patients who were prescribed a new potentially inappropriate medication use following discharge (n=4452, 53.4%, (95% CI 52.4-54.4)) and those who continued without filling a potentially inappropriate prescription (n=5094, 46.7%, (95% CI 45.6-47.6)). Patients with prescriptions for new potentially inappropriate medication were less likely to use multi-dose dispensing services (36.9% vs. 41.3%) and used a slightly higher number of medications both prior to admission and post-discharge (median [IQR] of 4 [2-7] vs. 3 [0-6]). Post-discharge, the median number of medications was substantially higher amongst those patients with new potentially inappropriate prescriptions ([IQR] 9 [6-13] vs 4 [1-7]). They were also more likely to have a higher risk score for the likelihood of experiencing medication-related harm post-discharge, median [IQR] 10.70[7.17-14.54] vs. 10.20 [7.44-15.30]).

Additionally, patients with new potentially inappropriate prescription were more likely to receive a diagnosis of an adverse drug reaction post-discharge (4.3% vs. 2.2%). The comorbidity and frailty burden was comparable, as well as the distribution between admitting internal medicine sub-specialties except for geriatrics, where patients were less likely to be prescribed new potentially inappropriate medication (6.3% vs. 5.1%).

After adjustment for comorbidities and admission information, multi-dose dispensing service (OR 1.26,95% CI 1.15-1.39), dementia (OR 1.29, 95% CI 1.01-1.65), pre-admission polypharmacy (OR 1.45,95% CI 1.32-1.60) and hyper-polypharmacy (OR 1.38,95% CI 1.22-1.59), were associated with higher odds of new potentially inappropriate medication use after discharge, but admission to internal medicine followed by transfer to geriatrics was associated with lower odds (OR 0.80, 95% CI 0.67-1.39), (Figure 1).

Figure 2 shows the prevalence of potentially inappropriate medication across different burden of pre-admission polypharmacy. Amongst patients with non-polypharmacy, the prevalence of potentially inappropriate medication use was 34.0% (95% CI 33.1-35.0) among patients with polypharmacy, it was 77.7%, (95% Cl 76.9-78.4)) and among patients with hyper-polypharmacy, it was 96.4% (95% Cl 96.2-96.6).

An unadjusted restricted cubic spline analysis revealed a non-linear relationship between the absolute number of different medications filled in the year preceding admission and the prevalence of potentially inappropriate medication use based on the Beers criteria. Figure 3 shows the relationship between the absolute number of filled medications and the prevalence of potentially inappropriate medication by organ system or therapeutic category. Amongst categories of potentially inappropriate medication use, patients most filled medications that act on the central nervous and gastrointestinal system. When medications within these two organ systems were further analysed, a strong relationship was identified between increased pre-admission polypharmacy and the likelihood of having a prescription for benzodiazepines and Z-drugs (Figure S_2), and medications that act on the gastrointestinal system, in particular proton pump inhibitors (Figure S_3).

Table S_1 compares which Beers criteria subgroup were met for the whole cohort separated on varying degrees of polypharmacy prior to admission. The most commonly met Beers criteria in the whole cohort in the year prior to admission was for medications that act on the central nervous system (59.2%), most commonly z-drugs (43.1%), and benzodiazepines (31.2%). The second most common Beers criteria the cohort met was due to gastrointestinal medications (48.4%), most commonly proton pump inhibitors (45.8%).

Following discharge, the most frequently added medication that met Beers criteria were proton pump inhibitors (15.3%), Z-drugs (9.2%), benzodiazepines (8.9%), anti-psychotics (6.6%), anti-cholinergic (5.4%), cardiovascular (5.2%) and antihistamine (5.0%) medications.

Discussion

We identified that pre-admission and post-discharge potentially inappropriate medication use among internal medicine patients is widespread and correlated with increasing pre-admission polypharmacy. Interestingly, no correlation was found between potentially inappropriate medication use and clinical outcomes, such as short- and long-term mortality, length of hospitalization, and 30-day readmission rate. This contradicts our secondary hypothesis that potentially inappropriate medication use was correlated with adverse clinical outcomes, while residual confounding is also possible.

Few studies have focused on hospitalized internal medicine patients. Our study estimated that the prevalence of patients with any pre-admission potentially inappropriate medication use was 82.7%, which is in line with a recent inpatient cohort study where the prevalence in older individuals was reported to be 92% according to the same Beers criteria.[14] In the latest version of Beers criteria published in 2023, there were notable updates, such as categorizing aspirin and rivaroxaban as medications to be avoided. Most other changes involved strengthening existing criteria with new evidence or clarifying language, which should not impact the findings of this study.[15]

Additionally, hospitalized patients represent a different cohort from a generalized outpatient cohort where a recent meta-analysis considered that the prevalence of potentially inappropriate medication use worldwide ranged from 1.3% to 95.2%, with a pooled prevalence estimate of 36.7%.[16] Likely reasons for higher prevalence and incidence in our study population are very different cohorts since our hospital-based cohort is likely to be older, with greater multimorbidity and more medications compared with outpatient and community-based cohorts.

This study identified a correlation between the female gender and potentially inappropriate medication use (51.7% vs 48.3%), which is in accordance with previous studies.[8,17] Additionally, our study reports a link between the use of multidose-dispensing services and potentially inappropriate medication use, which is in line with previous studies.[18] These findings raise concerns as the use of multidose dispensing services, is often assumed to aid when concerns arise regarding compliance and

complex medication use. However, our study implies that it could contribute towards both polypharmacy and potentially inappropriate medication use. However, a new multidose dispensing service initiated during hospital admission can be problematic as new medications are often being trailed and need to be altered or stopped shortly after discharge. This aligns poorly with long-term prescriptions that multidose dispensing services providers prefer, at least in our hospital system. It is prudent that there should be a mandate for a review by their primary care physicians prior to prescriptions of a longer duration with a frequent review to assess medication appropriateness.

Admission to geriatric ward was associated with reduced odds of developing new, potentially inappropriate medication use post-discharge. This is potentially because healthcare professionals working in geriatric care are likely to have the knowledge and skills to identify inappropriate medication use and its potential harm for older patients and, therefore, be less likely to initiate new inappropriate medications. This highlights the importance of judicious prescribing during hospitalization and the need to upskill non-specialized areas in managing older adults. The most common potentially inappropriate medications used in this study were medications acting on the central nervous system, with z-drug the most commonly prescribed medication, followed by benzodiazepines. This is in line with a recent cohort study applying Beers criteria in a cohort of evaluating internal medicine patients where the most frequently potentially inappropriate prescriptions were benzodiazepines. The difference between studies may be due to different prescription practices between the countries. Iceland, for example, has reported higher usage of medications acting on the nervous system compared to other countries. [19]

Several studies have identified interventions to address polypharmacy, potentially inappropriate medication use, and deprescribing opportunities.[20,21] A recent meta-analysis concluded that pharmaceutical interventions can improve prognosis in older adults by reducing polypharmacy, readmission rate, and the incidence of potentially inappropriate medication use. [20] However, there has to be a benchmark to address the potentially inappropriate use of medications, and likely, there will be no single solution. Ideally, patients at increased risk of potentially inappropriate medication use

should be followed up after a hospital admission by their healthcare provider. However, the risk of potentially inappropriate medication use must be evaluated individually, and the use of potentially inappropriate medication may be appropriate when other possibilities like non-pharmacological approaches or medications with less risks are not available or the benefit in the alleviation of symptoms is great enough.

Contrary to the findings of numerous studies [22,23], this study did not find a correlation between potentially inappropriate medication use and clinical outcomes, such as length of stay, readmission within 30 days, and mortality within 30 days. One reason for this may be the fact that both patient groups had similar burdens of comorbidity. However, it is also worth mentioning that clinical outcomes are multifactorial, and they are often dependent upon what support the patient has in the community. Additionally, we observed a correlation with the likelihood of being diagnosed with an adverse drug event post-discharge. This is in line with previous research. [24]

The current study has several strengths. A centralized nationwide Prescription Medicine Registry was used that allows detailed information, which includes over 95% of all prescriptions in the country, and the ability to link different registries to collect information. The large number of participants included in an extensive database had a complete follow-up for clinical outcomes and with no loss of follow-up of patients.

A limitation is the dependence on using filled medications based on the prescription registry database. This method may overestimate the number of medications the participants take, as adherence still needs to be determined. Additionally, assessing comorbidity burden using diagnoses from hospital and primary care settings risks underreporting true comorbidities or their severity.

Conclusion

In conclusion, pre-admission and post-discharge potentially inappropriate medication use is common among internal medicine patients, and there is a correlation between polypharmacy and the increased likelihood of potentially inappropriate medication use. Specific sub-groups were at a more risk of

developing increased potentially inappropriate medication use after discharge, while patients admitted to geriatrics had decreased risk. This demonstrates the need for an increased follow-up, medication review, and deprescribing following hospital discharge. Emphasis should be put on supporting the transition of care and providing information to patients, caregivers, and primary care physicians regarding the changes in medication during the hospital stay. A potential focus could be on those medications that should be used short-term or new medicines that should be re-evaluated shortly after discharge.

References

1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC geriatrics*. Oct 10 2017;17(1):230. doi:10.1186/s12877-017-0621-2
2. Gnjidic D, Hilmer SN, Blyth FM, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. *Clinical pharmacology and therapeutics*. Mar 2012;91(3):521-8. doi:10.1038/clpt.2011.258
3. Stevenson JM, Davies JG, Martin FC. Medication-related harm: a geriatric syndrome. *Age and ageing*. Dec 1 2019;49(1):7-11. doi:10.1093/ageing/afz121
4. Stevenson JM, Williams JL, Burnham TG, et al. Predicting adverse drug reactions in older adults; a systematic review of the risk prediction models. *Clinical interventions in aging*. 2014;9:1581-93. doi:10.2147/cia.S65475
5. Naik H, Murray TM, Khan M, et al. Population-Based Trends in Complexity of Hospital Inpatients. *JAMA Intern Med*. Feb 1 2024;184(2):183-192. doi:10.1001/jamainternmed.2023.7410
6. Guaraldo L, Cano FG, Damasceno GS, Rozenfeld S. Inappropriate medication use among the elderly: a systematic review of administrative databases. *BMC geriatrics*. Nov 30 2011;11:79. doi:10.1186/1471-2318-11-79
7. Taghy N, Cambon L, Cohen JM, Dussart C. Failure to Reach a Consensus in Polypharmacy Definition: An Obstacle to Measuring Risks and Impacts-Results of a Literature Review. *Therapeutics and clinical risk management*. 2020;16:57-73. doi:10.2147/tcrm.S214187
8. 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*. Apr-Jun 2019;17(2):1439. doi:10.18549/PharmPract.2019.2.1439
9. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Archives of internal medicine*. Jul 28 1997;157(14):1531-6.
10. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*. Apr 2019;67(4):674-694. doi:10.1111/jgs.15767
11. 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*. Mar 28 2024;14(3):e078890. doi:10.1136/bmjopen-2023-078890
12. 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;85:867-872.
13. Gunnarsdottir GM, Helgadottir S, Einarsson SG, et al. Validation of the Hospital Frailty Risk Score in older surgical patients: A population-based retrospective cohort study. *Acta anaesthesiologica Scandinavica*. Sep 2021;65(8):1033-1042. doi:10.1111/aas.13837
14. Perpétuo C, Plácido AI, Rodrigues D, et al. Prescription of Potentially Inappropriate Medication in Older Inpatients of an Internal Medicine Ward: Concordance and Overlap Among the EU(7)-PIM List and Beers and STOPP Criteria. *Frontiers in pharmacology*. 2021;12:676020. doi:10.3389/fphar.2021.676020
15. Panel AGSBCUE. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*. 2023;71(7):2052-2081.
16. 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*. Aug 1 2023;6(8):e2326910. doi:10.1001/jamanetworkopen.2023.26910
17. Alwhaibi M, Balkhi B. Gender Differences in Potentially Inappropriate Medication Use among Older Adults. *Pharmaceuticals (Basel)*. Jun 12 2023;16(6)doi:10.3390/ph16060869

18. Sjöberg C, Edward C, Fastbom J, et al. Association between multi-dose drug dispensing and quality of drug treatment--a register-based study. *PloS one*. 2011;6(10):e26574. doi:10.1371/journal.pone.0026574
19. Højlund M, Gudmundsson LS, Andersen JH, et al. Use of benzodiazepines and benzodiazepine-related drugs in the Nordic countries between 2000 and 2020. *Basic Clin Pharmacol Toxicol*. Jan 2023;132(1):60-70. doi:10.1111/bcpt.13811
20. Zhou S, Li R, Zhang X, et al. The effects of pharmaceutical interventions on potentially inappropriate medications in older patients: a systematic review and meta-analysis. *Front Public Health*. 2023;11:1154048. doi:10.3389/fpubh.2023.1154048
21. van Poelgeest E, Seppala L, Bahat G, et al. Optimizing pharmacotherapy and deprescribing strategies in older adults living with multimorbidity and polypharmacy: EuGMS SIG on pharmacology position paper. *Eur Geriatr Med*. Oct 9 2023;doi:10.1007/s41999-023-00872-0
22. Counter D, Millar JWT, McLay JS. Hospital readmissions, mortality and potentially inappropriate prescribing: a retrospective study of older adults discharged from hospital. *British journal of clinical pharmacology*. Aug 2018;84(8):1757-1763. doi:10.1111/bcp.13607
23. Sehgal V, Bajwa SJS, Sehgal R, Bajaj A, Khaira U, Kresse V. Polypharmacy and potentially inappropriate medication use as the precipitating factor in readmissions to the hospital. *Journal of family medicine and primary care*. 2013;2(2):194.
24. Weir DL, Lee TC, McDonald EG, et al. Both New and Chronic Potentially Inappropriate Medications Continued at Hospital Discharge Are Associated With Increased Risk of Adverse Events. *Journal of the American Geriatrics Society*. Jun 2020;68(6):1184-1192. doi:10.1111/jgs.16413

Figure Legends

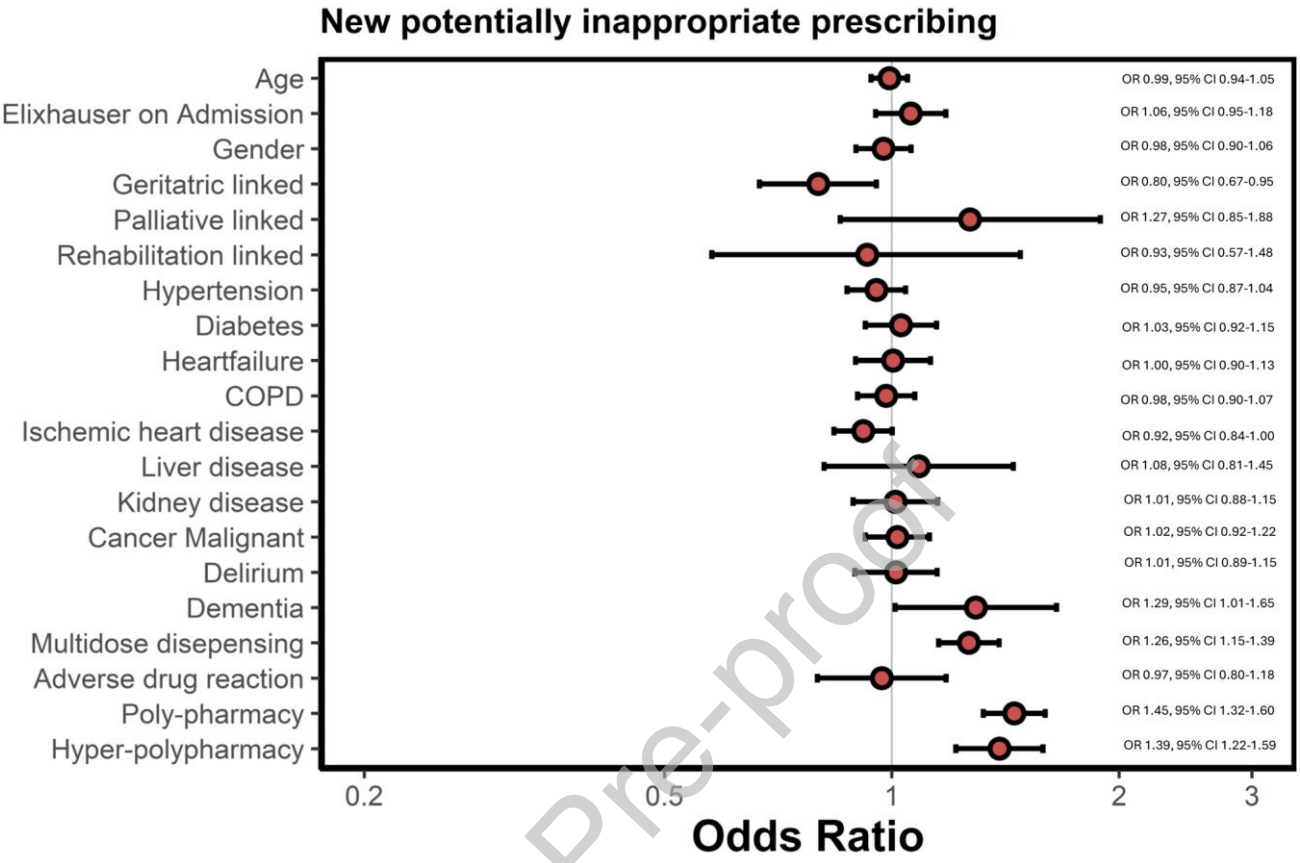


Figure 1. The results of a multivariable regression model of the risk factors of receiving a new prescription for a potentially inappropriate medication in the year following admission using age, sex (female compared with male), admitting specialty (compared with general medicine), Elixhauser comorbidity index class (compared with <1), individual comorbidities, 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 fall or adverse drug reaction diagnosis prior to admission, as covariates.

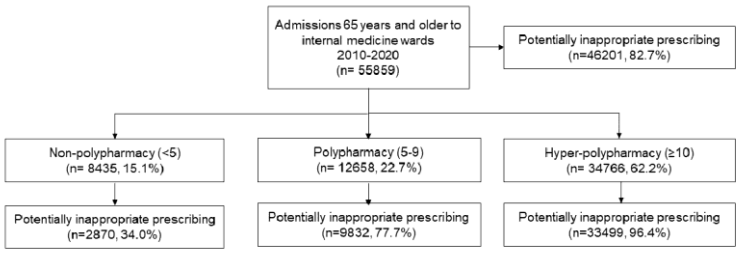


Figure 2

A consort diagram of participant inclusion, level of polypharmacy based on the number of different medications filled in the year preceding admission by internal medicine (<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.

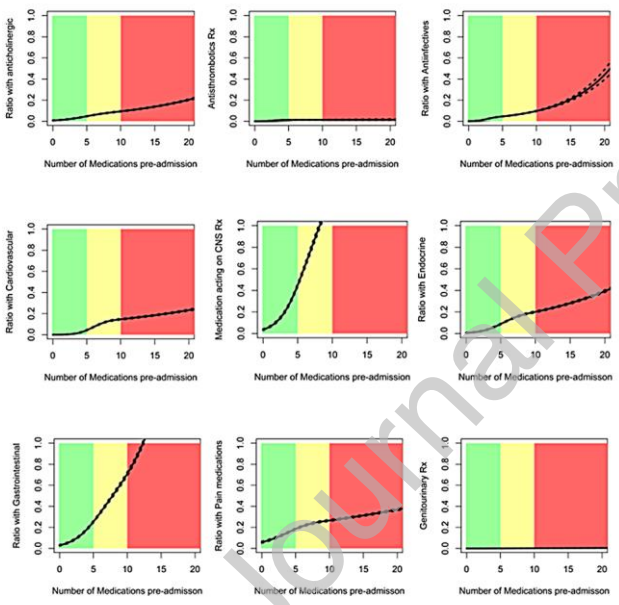


Figure 3.

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

Tables

Table 1.

Patient characteristics for patients who filled a prescription for a potentially inappropriate medication use based on the 2019 Beers criteria pre-admission. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No potentially inappropriate medication use pre-admission	Potentially inappropriate medication use pre-admission	All patients	p
Total number of patients	9546 (17.1%)	46313 (82.9%)	55859	
Sex (male)	4748 (49.7)	22371 (48.3)	27119 (48.5)	0.044
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 86.00]	80.00 [73.00, 86.00]	0.055
Multi-dose dispensing services	3129 (32.8)	27376 (59.1)	30505 (54.6)	<0.001
Number of pre-admission medications (median [IQR])	4.00 [1.00, 7.00]	13.00 [9.00, 19.00]	12.00 [7.00, 17.00]	<0.001
Number of post-discharge medications (median [IQR])	6.00 [3.00, 10.00]	13.00 [8.00, 18.00]	12.00 [7.00, 17.00]	<0.001
Elixhauser Comorbidity Index [IQR])	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	8.00 [3.00, 14.00]	0.305
(<1]	1882 (19.7)	9079 (19.6)	10961 (19.6)	0.495
(1-4]	1351 (14.2)	6298 (13.6)	7649 (13.7)	
(4-5]	700 (7.3)	3467 (7.5)	4167 (7.5)	
(5-8]	1229 (12.9)	5785 (12.5)	7014 (12.6)	
(>8]	4384 (45.9)	21684 (46.8)	26068 (46.7)	
Hospital Frailty Risk Score Class				0.749
Low (< 5)	2707 (28.4)	12910 (27.9)	15617 (28.0)	
Med (5-15)	4654 (48.8)	22690 (49.0)	27344 (49.0)	
High (> 15)	2185 (22.9)	10713 (23.1)	12898 (23.1)	
Individual comorbidities				
Ischemic heart disease	3927 (41.1)	18879 (40.8)	22806 (40.8)	0.506
Congestive heart failure	2687 (28.1)	12793 (27.6)	15480 (27.7)	0.075
Hypertension	6307 (66.1)	30467 (65.8)	36774 (65.8)	0.602
Diabetes Mellitus	1754 (18.4)	8766 (18.9)	10520 (18.8)	0.213
Chronic obstructive pulmonary disease	3439 (36.0)	17135 (37.0)	20574 (36.8)	0.075
Liver disease	198 (2.1)	1171 (2.5)	1369 (2.5)	0.010
Chronic kidney disease	1261 (13.2)	6240 (13.5)	7501 (13.4)	0.502
Malignant neoplasm	2675 (28.0)	12605 (27.2)	15280 (27.4)	0.111
Psychiatric	1606 (16.8)	7604 (16.4)	9210 (16.5)	0.339
Dementia	280 (2.9)	1431 (3.1)	1711 (3.1)	0.438
Delerium	1213 (12.7)	5742 (12.4)	6955 (12.5)	0.415
Internal Medicine Specialty				0.025
Cardiology	2216 (23.2)	10413 (22.5)	12629 (22.6)	
Dermatology	30 (0.3)	152 (0.3)	182 (0.3)	

Endocrinology	147 (1.5)	701 (1.5)	848 (1.5)	
Gastroenterology	634 (6.6)	3164 (6.8)	3798 (6.8)	
General internal medicine	1247 (13.1)	6275 (13.5)	7522 (13.5)	
Geriatrics	1157 (12.1)	6062 (13.1)	7219 (12.9)	
Hematology	411 (4.3)	1938 (4.2)	2349 (4.2)	
Infectious diseases	454 (4.8)	2155 (4.7)	2609 (4.7)	
Nephrology	235 (2.5)	1107 (2.4)	1342 (2.4)	
Neurology	707 (7.4)	3041 (6.6)	3748 (6.7)	
Oncology	496 (5.2)	2362 (5.1)	2858 (5.1)	
Palliative care	162 (1.7)	836 (1.8)	998 (1.8)	
Pulmonology	1111 (11.6)	5219 (11.3)	6330 (11.3)	
Rehabilitation	43 (0.5)	282 (0.6)	325 (0.6)	
Rheumatology	496 (5.2)	2606 (5.6)	3102 (5.6)	
Admissions linked with primary admission				
Geriatrics	551 (5.8)	2590 (5.6)	3141 (5.6)	0.454
Palliative care	103 (1.1)	467 (1.0)	570 (1.0)	0.660
Rehabilitation	73 (0.8)	301 (0.7)	374 (0.7)	0.282
Intensive care unit admission	410 (4.3)	1928 (4.2)	2338 (4.2)	0.566
Clinical Outcomes				
Fall diagnosis post-discharge	16 (0.2)	128 (0.3)	144 (0.3)	0.064
Length of hospital stay (days)	7.00 [3.00, 15.00]	7.00 [3.00, 15.00]	7.00 [3.00, 15.00]	0.244
Diagnosis of adverse drug reaction pre-admission (%)	431 (4.5)	5684 (12.3)	6115 (10.9)	<0.001
Diagnosis of adverse drug reaction post-discharge (%)	305 (3.2)	3100 (6.7)	3405 (6.1)	<0.001
Next admission (median [IQR]	131.00 [29.00, 463.00]	132.00 [29.00, 455.00]	132.00 [29.00, 456.00]	0.609
Mortality 30 days (%)	392 (4.1)	2033 (4.4)	4354 (7.8)	0.227
Readmission within 30 days (%)	1486 (15.6)	7146 (15.4)	8632 (15.5)	0.748

Table 2.

Comparison of patients with no potentially inappropriate medication use pre-admission or post-discharge to patients with no potentially inappropriate medication use pre-admission but new potentially inappropriate medication use post-discharge. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No potentially inappropriate medication use pre-admission nor new potentially inappropriate medication use post-discharge	New potentially inappropriate medication use post-discharge and but not pre-admission	p
Total number of patients	5094	4452	
Sex (male)	2516 (49.4)	2232 (50.1)	0.481
Age median [IQR]), years	80.00 [73.00, 85.00]	80.00 [73.00, 85.00]	0.526
Multi-dose dispensing services	2690 (41.3)	1643 (36.9)	<0.001
Number of pre-admission medications (median [IQR])	3.00 [0.00, 6.00]	4.00 [2.00, 7.00]	<0.001
Number of post-discharge medications (median [IQR])	4.00 [1.00, 7.00]	9.00 [6.00, 13.00]	<0.001
Number of pre-admission medications without antibiotics (median [IQR])	2.00 [0.00, 6.00]	4.00 [1.00, 6.00]	<0.001
Elixhauser Comorbidity Index [IQR])			
(<1]	987 (19.4)	895 (20.1)	0.328
(1-4]	722 (14.2)	629 (14.1)	
(4-5]	388 (7.6)	312 (7.0)	
(5-8]	682 (13.4)	547 (12.3)	
(>8]	2315 (45.4)	2069 (46.5)	
Hospital Frailty Risk Score Class			0.659
Low (< 5)	1427 (28.0)	1280 (28.8)	
Med (5-15)	2504 (49.2)	2150 (48.3)	
High (> 15)	1163 (22.8)	1022 (23.0)	
Individual Comorbidities			
Ischemic heart disease	2140 (42.0)	1787 (40.1)	0.067
Congestive heart failure	1432 (28.1)	1255 (28.2)	0.951
Hypertension	3392 (66.6)	2915 (65.5)	0.261
Diabetes Mellitus	1841 (36.1	822 (18.5)	0.854
Chronic obstructive pulmonary disease	18976 (36.9)	1598 (35.9)	0.819
Liver disease	101 (2.0)	97 (2.2)	0.549
Chronic kidney disease	669 (13.1)	592 (13.3)	0.837
Malignant neoplasm	1407 (27.6)	1268 (28.5)	0.362
Psychiatric	836 (16.4)	770 (17.3)	0.261
Dementia	133 (2.6)	147 (3.3)	0.053
Delerium	643 (12.6)	570 (12.8)	0.815
Internal Medicine Specialty			0.747
Cardiology	1189 (23.3)	1027 (23.1)	
Dermatology	15 (0.3)	15 (0.3)	

Endocrinology	76 (1.5)	71 (1.6)	
Gastroenterology	327 (6.4)	307 (6.9)	
General internal medicine	666 (13.1)	581 (13.1)	
Geriatrics	633 (12.4)	524 (11.8)	
Hematology	226 (4.4)	185 (4.2)	
Infectious diseases	248 (4.9)	206 (4.6)	
Nephrology	120 (2.4)	115 (2.6)	
Neurology	365 (7.2)	342 (7.7)	
Oncology	254 (5.0)	242 (5.4)	
Palliative care	80 (1.6)	82 (1.8)	
Pulmonology	592 (11.6)	519 (11.7)	
Rehabilitation	29 (0.6)	14 (0.3)	
Rheumatology	274 (5.4)	222 (5.0)	
Admissions linked with primary admission			
Geriatrics	323 (6.3)	228 (5.1)	0.012
Palliative care	49 (1.0)	54 (1.2)	0.278
Rehabilitation	40 (0.8)	33 (0.7)	0.898
Intensive care unit admission	113 (2.2)	192 (4.3)	0.977
Clinical Outcomes			
Length of hospital stay (days)	7.00 [3.00, 15.00]	7.00 [3.00, 14.00]	0.024
Diagnosis of adverse drug reaction pre-admission (%)	223 (4.4)	208 (4.7)	0.521
Diagnosis of adverse drug reaction post-discharge (%)	114 (2.2)	191 (4.3)	<0.001
Next admission (median [IQR]	133.00 [29.00, 461.50	125.00 [28.00, 461.00]	0.994
Mortality 30 days (%)	388 (7.6)	360 (8.1)	0.416
Readmission within 30 days (%)	796 (15.6)	690 (15.5)	0.947

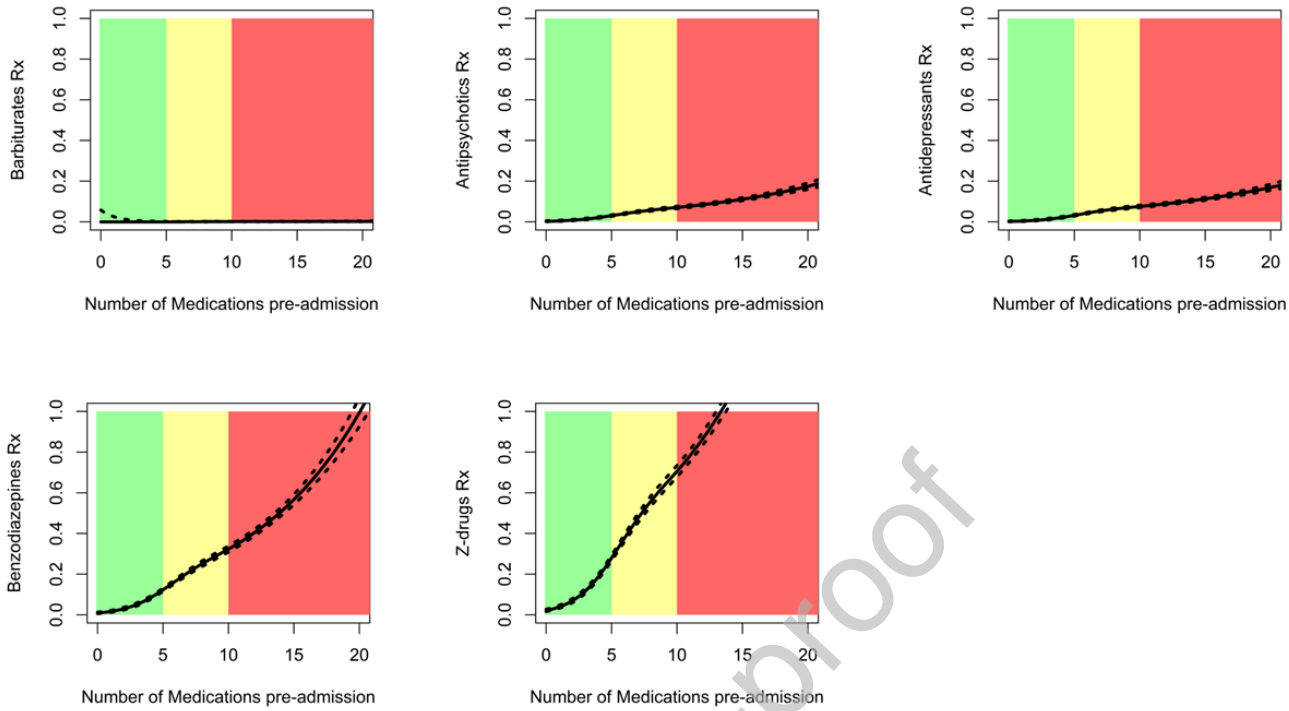
Clinical significance

- The greater the number of medications prescribed to patients, the more likely there will be a potentially inappropriate medication.
- There is a link between multidose-dispensing services and potentially inappropriate medication use.
- Inpatients admitted to or transferred to a geriatric ward have less risk of a prescribed inappropriate medication upon discharge.
- Inpatients at increased risk of potentially inappropriate medication use should have their medications reviewed by healthcare providers soon after discharge.

Appendix A. Supplementary data

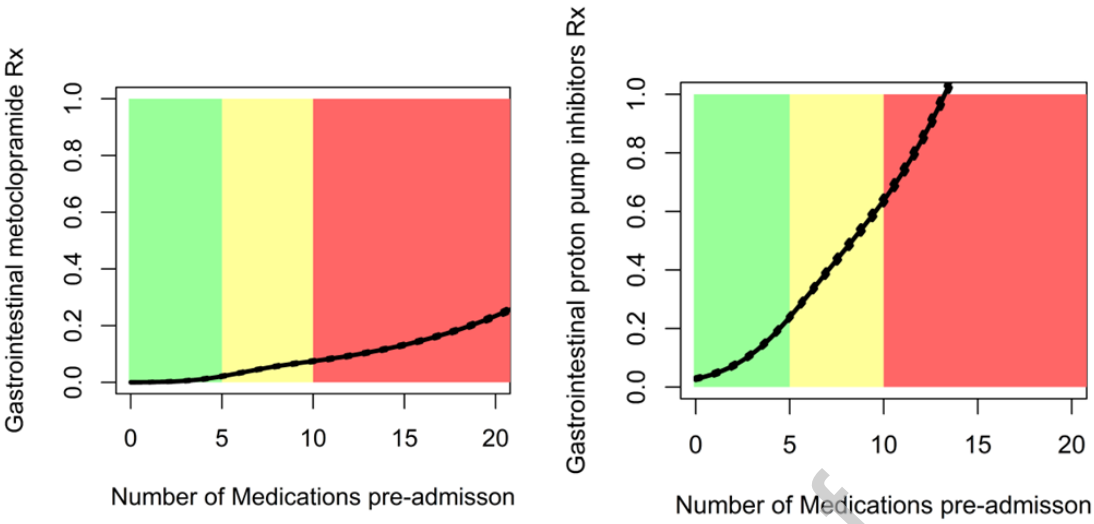
Supplementary Figure 1

The prevalence of potentially inappropriate medication (PIM) use based on 2019 Beers criteria based on medications filled in the year preceding admission by internal medicine (non-potentially inappropriate medication use = green and potentially inappropriate medication use = red).



Supplementary Figure 2

The association between the number of medications pre-admission and risk of potentially inappropriate medication use and the 2019 Beers criteria for specific medications acting on the central nervous system. 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 admission by internal medicine.



Supplementary Figure 3

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. 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 admission by internal medicine.

Supplementary Table 1

The table shows the subcategories of Beers Criteria filled, based on 2019 Beers criteria based on the patients pre-admission polypharmacy burden estimated by the number of different medications filled in the year preceding admission (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy). Values are presented as count (%) or median (IQR) unless specified otherwise.

	Non-Polypharmacy pre-admission	Polypharmacy pre-admission	Hyper-Polypharmacy pre-admission	All patients pre-admission	P-value
Total number of patients	8435 (15.1)	12658 (22.7)	34766 (62.2)	55859	
Age (median [IQR]), years	74.00 [69.00, 80.00]	74.00 [69.00, 80.00]	76.00 [71.00, 82.00]	80.00 [73.00, 86.00]	<0.001
[65,75)	2594 (31.1)	3724 (29.8)	10530 (30.6)	16848 (30.5)	
[75,85)	3360 (40.3)	5207 (41.7)	13879 (40.4)	22446 (40.7)	
[85,95.)	2384 (28.6)	3563 (28.5)	9954 (29.0)	15901 (28.8)	
Beers criteria total score pre-admission (median [IQR])	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	4.00 [2.00, 5.00]	3.00 [1.00, 4.00]	<0.001
Beers criteria anticholinergics (%)	199 (2.4)	794 (6.3)	5302 (15.3)	6295 (11.3)	<0.001
Beers criteria Anticholinergics (antihistamines) (%)	179 (2.1)	730 (5.8)	4981 (14.3)	5890 (10.5)	<0.001
Beers criteria Anticholinergics (antiparkinsonian) (%)	15 (0.2)	45 (0.4)	198 (0.6)	258 (0.5)	0.017
Beers criteria Anticholinergics (antispasmodics) (%)	5 (0.1)	24 (0.2)	232 (0.7)	261 (0.5)	<0.001
Beers criteria antithrombotic (%)	14 (0.2)	123 (1.0)	485 (1.4)	622 (1.1)	<0.001
Beers criteria anti-infective (%)	46 (0.5)	342 (2.7)	2880 (8.3)	3268 (5.9)	<0.001
Beers criteria cardiovascular (%)	75 (0.9)	859 (6.8)	6336 (18.2)	7270 (13.0)	<0.001
Beers criteria (cardiovascular peripheral alpha) (%)	9 (0.1)	103 (0.8)	802 (2.3)	914 (1.6)	<0.001
Beers criteria (cardiovascular central alpha) (%)	0 (0.0)	1 (0.0)	9 (0.0)	10 (0.0)	0.178
Beers criteria (cardiovascular disopyramide) (%)	6 (0.1)	32 (0.3)	110 (0.3)	148 (0.3)	<0.001
Beers criteria (cardiovascular dronedarone) (%)	2 (0.0)	38 (0.3)	148 (0.4)	188 (0.3)	<0.001
Beers criteria (cardiovascular digoxin) (%)	29 (0.3)	369 (2.9)	3152 (9.1)	3550 (6.4)	<0.001
Beers criteria (cardiovascular nifedipine) (%)	10 (0.1)	95 (0.8)	486 (1.4)	591 (1.1)	<0.001
Beers criteria (cardiovascular amiodarone) (%)	21 (0.2)	261 (2.1)	2411 (6.9)	2693 (4.8)	<0.001
Beers criteria central nervous system (%)	1102 (13.1)	5406 (42.7)	26550 (76.4)	33058 (59.2)	<0.001

Beers criteria (central nervous system antidepressant) (%)	105 (1.2)	575 (4.5)	3668 (10.6)	4348 (7.8)	<0.001
Beers criteria (central nervous system antipsychotics) (%)	243 (2.9)	1131 (8.9)	6503 (18.7)	7877 (14.1)	<0.001
Beers criteria (central nervous system barbiturates) (%)	1 (0.0)	36 (0.3)	136 (0.4)	173 (0.3)	<0.001
Beers criteria (central nervous system benzodiazepines) (%)	369 (4.4)	2088 (16.5)	14965 (43.0)	17422 (31.2)	<0.001
Beers criteria (central nervous system z-drugs) (%)	539 (6.4)	3338 (26.4)	20183 (58.1)	24060 (43.1)	<0.001
Beers criteria endocrine (%)	250 (3.0)	1450 (11.5)	8974 (25.8)	10674 (19.1)	<0.001
Beers criteria (endocrine androgens) (%)	24 (0.3)	114 (0.9)	713 (2.1)	851 (1.5)	<0.001
Beers criteria (endocrine desiccated thyroid) (%)	1 (0.0)	0 (0.0)	11 (0.0)	12 (0.0)	0.093
Beers criteria (endocrine estrogens) (%)	112 (1.3)	591 (4.7)	4082 (11.7)	4785 (8.6)	<0.001
Beers (endocrine growth hormone) (%)	1 (0.0)	9 (0.1)	21 (0.1)	31 (0.1)	0.165
Beers criteria (endocrine megestrol) (%)	1 (0.0)	2 (0.0)	12 (0.0)	15 (0.0)	0.360
Beers criteria (endocrine sulfonylurea) (%)	113 (1.3)	769 (6.1)	4665 (13.4)	5547 (9.9)	<0.001
Beers criteria gastrointestinal (%)	770 (9.1)	3669 (29.0)	22579 (64.9)	27018 (48.4)	<0.001
Beers criteria (gastrointestinal metoclopramide) (%)	46 (0.5)	455 (3.6)	5936 (17.1)	6437 (11.5)	<0.001
Beers criteria (gastrointestinal proton pump inhibitors) (%)	735 (8.7)	3418 (27.0)	21448 (61.7)	25601 (45.8)	<0.001
Beers criteria Pain medications (%)	929 (11.0)	2384 (18.8)	8694 (25.0)	12007 (21.5)	<0.001
Beers criteria (pain medications meperidine (%)	0 (0.0)	0 (0.0)	3 (0.0)	3 (0.0)	0.402
Beers criteria pain medications nonselective NSAID (%)	875 (10.4)	2230 (17.6)	7713 (22.2)	10818 (19.4)	<0.001
Beers criteria (pain medications skeletal muscle relaxant) (%)	81 (1.0)	266 (2.1)	1577 (4.5)	1924 (3.4)	<0.001
Beers criteria (genitourinary) (%)	2 (0.0)	21 (0.2)	129 (0.4)	152 (0.3)	<0.001