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Potentially inappropriate prescribing according to STOPP and START and adverse outcomes in community-dwelling older people: a prospective cohort study.

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Structured summary

Aims

This study aims to determine if potentially inappropriate prescribing (PIP) is associated with increased healthcare utilisation, functional decline and reduced quality of life (QoL) in a community-dwelling older cohort.

Method

This prospective cohort study included participants aged ≥65 years from The Irish Longitudinal Study on Ageing (TILDA) with linked administrative pharmacy claims data who were followed up after two years. PIP was defined by the Screening Tool for Older Persons Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START). The association with number of emergency department (ED) visits and GP visits reported over 12 months was analysed using multivariate negative binomial regression adjusting for confounders. Marginal structural models investigated the presence of time-dependent confounding.

Results

Of participants followed up (n=1,753), PIP was detected in 57% by STOPP and 41.8% by START, 21.7% reported an ED visit and 96.1% visited a GP (median 4, IQR 2.5-6). Those with any STOPP criterion had higher rates of ED visits (adjusted incident rate ratio (IRR) 1.30, 95% confidence interval (CI) 1.02-1.66) and GP visits (IRR 1.15, 95%CI 1.06-1.24). Patients with two or more START criteria had significantly more ED visits (IRR 1.45, 95%CI 1.03-2.04) and GP visits (IRR 1.13, 95%CI 1.01-1.27) than people with no criteria. Adjusting for time-dependent confounding did not affect the findings.

Conclusions

Both STOPP and START were independently associated with increased healthcare utilisation and START was also related to functional decline and QoL. Optimising prescribing to reduce PIP may provide an improvement in patient outcomes.

Section 1: What is already known about this subject:

- Potentially inappropriate medicines and potential prescribing omissions are common issues in older people.
- Evidence of a link between these process measures of care and patient outcomes is important.
- Many studies to date have been hospital-based and cross-sectional and evidence of an effect on patient-centred outcomes is less clear.

Section 2: What this study adds:

- In this community-dwelling older cohort, potentially inappropriate medicines were associated with increased emergency departments and GP visits.
- Patients with multiple potential prescribing omissions had higher healthcare utilisation, increased chance of functional decline and reduced quality of life.
- Optimising treatment to address potentially inappropriate prescribing may improve outcomes for older people

Introduction

Older people are particularly vulnerable to adverse effects from medicines, partly due to pharmacokinetic and pharmacodynamic changes in ageing, and also because multimorbidity and complex drug regimens involving multiple medicines (polypharmacy) are common in this age group.[1–3] This has led to concerns regarding potentially inappropriate prescribing (PIP) in older people, including both errors of commission and omission.[4] The first form of PIP refers to potentially inappropriate medicines (PIMs), the use of medicines in circumstances where the risks outweigh the benefits or where a safer or better alternative exists. The second form of PIP is potential prescribing omissions (PPOs), medications which are clinically indicated for a patient not being prescribed. A number of explicit criteria have been developed to identify PIP and two commonly used measures are the Screening Tool for Older Persons' Prescriptions (STOPP) which focuses on PIMs, and the Screening Tool to Alert doctors to Right Treatment (START) to screen for PPOs. [5]

While STOPP and START can be considered process measures of medication safety,[6] it is important to establish that such prescribing does have an effect on patient outcomes, such as adverse drug events (ADEs), hospitalisations or quality of life (QoL). A number of studies have assessed the association of STOPP PIMs with such outcomes; however the impact of START PPOs on patients has received little attention.[7] Much of this research has been cross-sectional with limited capacity to determine the prospective relationship of PIMs and PPOs with patient outcomes. It is difficult to establish whether an association is causal using such study designs due to potential bias and confounding. Longitudinal cohort studies provide a more robust method to assess the impact of medication exposure as they can account for confounding by time-varying factors using appropriate methods and may allow for inference of causal effects.[8]

The aim of this study is to determine the association of potentially inappropriate prescribing detected by STOPP and START with healthcare utilisation, functional decline and QoL in a cohort of community-dwelling people aged ≥65 years in a longitudinal study.

Methods

Study design

This study included participants from The Irish Longitudinal Study on Ageing (TILDA), a nationally-representative cohort study charting the health, economic and social circumstances of community dwellers aged ≥50 years. Some TILDA participants also consented to use of their administrative pharmacy claims data from the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS). Participants were included in the present study if they were aged ≥65 years at baseline TILDA interview, had been followed up after two years, were eligible for the General Medical Services (GMS) scheme and provided an identifier which was successfully linked to their pharmacy claims data. The GMS scheme provides free health services and prescribed medicines to eligible persons in Ireland, however a small monthly co-payment of €0.50 per prescription item has applied since October 2010. Eligibility for the GMS scheme is based on means testing, although all people aged over 70 were eligible until December 2008 when a higher income threshold was introduced for this age group compared to the general population. However approximately 96% of this age group were still eligible in 2012.[9] The STROBE standardised reporting guidelines for cohort studies have been followed in the reporting of this research.[10]

Data collection for TILDA is conducted in waves every two years, including a face-to-face interview and self-completion questionnaire. Baseline data collection was carried out between 2009 and 2011 and participants were followed up from 2012 to 2013. Medication dispensing data were extracted from the HSE-PCRS pharmacy claims database for each participant in the present study from 15 months before the date of their TILDA baseline interview up to their follow-up interview to determine PIP exposure and all data were anonymised after extraction. Ethical approval for TILDA has been granted by Trinity College Dublin Faculty of Health Sciences research ethics committee.

Outcomes

The primary outcome under investigation was healthcare utilisation, including both hospital emergency department (ED) visits and general practitioner (GP) visits. Healthcare utilisation was assessed during TILDA interview by asking participants in the previous 12 months did they visit a hospital ED as a patient, and about how often they visited their GP. Regression models were fitted for ED visits and GP visits separately using the numbers of visits reported by participants in the 12 months preceding their follow-up interview as the dependent variables.

Two secondary outcomes were also analysed. The first was decline in physical functioning. Physical functioning is assessed during TILDA interview by asking participants if they have difficulty doing any of six named Activities of Daily Living (ADLs) due to a health or memory problem (including dressing, eating, and using the toilet). The outcome variable used was binary, classified as an increase in the number of ADLs a participant reported difficulty with between baseline and follow-up (functional decline) or no increase (no decline). Secondly QoL was investigated, which was assessed in the TILDA self-completion questionnaire using the CASP (Control, Autonomy, Self-Realisation, Pleasure), a measure designed for use in middle-aged and older people. In this analysis, participants' QoL score at follow-up measured using the CASP-R12, a revised 12 item version of CASP with a possible range from 0 (worst QoL) to 36 (best), [11] was included as the continuous outcome variable.

Exposure

Exposure to PIMs measured by STOPP and PPOs measured by START was determined in this cohort of TILDA participants with linked pharmacy claims data and was reported previously.[12] Briefly, 45 of 65 (69 %) STOPP criteria and 15 of 22 (68 %) START criteria were applied to determine the prevalence of PIP in the 12 months preceding baseline and follow-up interviews of TILDA (applicable criteria are listed in Table S1). The number of criteria that a participant was exposed to in each time period was determined separately for both screening tools. Exposure to STOPP for each participant

in the 12 months preceding outcome measurement and START exposure were included as the two main independent variables of interest.

Statistical analysis

Negative binomial regression models for the reported number of ED visits in 12 months and number of GP visits in 12 months were fitted, including two binary variables for the presence of any STOPP criteria and any START criteria (Model 1). Further analysis investigated a dose-response relationship by replacing these binary variables with categorical variables for 0, 1, or ≥2 criteria (Model 2). Results are presented as incident ratio ratios (IRR) with 95% confidence intervals (CI). This approach was then used for the secondary outcomes of functional decline using logistic regression models and QoL using linear regression models. Results of these analyses are presented as odds ratios (OR) and β regression coefficients respectively, with 95% CI. Models were adjusted for age group, gender, level of educational attainment as a measure of socicoeconomic status, living arrangements, number of repeat medicines and number of doctor-diagnosed chronic conditions (detailed variable description in Table S2). Specific covariates were also adjusted for in each model relating to the outcome of interest, for example, private health insurance status and number of ED/GP visits reported at baseline interview in the analysis of healthcare utilisation. The possibility of an additional effect in individuals exposed to both PIMs and PPOs was assessed by the addition of an interaction term to each model and likelihood ratio tests were used to evaluate if this improved model fit.

The impact of time-dependent confounding (by number of regular medicines or chronic conditions for example) was investigated using marginal structural models (MSMs), a two-step estimation strategy which separates confounding control for covariates that vary with time from parameter estimation.[8,13] For each participant two weights were calculated, (i) stabilised inverse probability weights, the inverse of the probability of having the PIP exposure they did conditional on past PIP exposure and covariate history (including measurements from both baseline and follow-up), and (ii)

censoring weights, the probability of remaining uncensored given past PIP exposure and covariate history. Weighted regression analyses (i.e. MSMs) were performed using the product of these weights for each outcome for STOPP PIM exposure and separately for START PPO exposure, adjusting for baseline covariates only. Statistical significance was assumed at $p<0.05$. Analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA).

Results

Participant inclusion in this study is shown in Figure 1 and a description of these individuals is included in Table 1. Those followed up (n=1,753) were mainly female (54.5%), had a mean age of 76.5 years (standard deviation (SD) 6), a median of 6 regular dispensed medicines and 3 reported doctor-diagnosed chronic conditions. Regarding PIP, 57% of participants had a STOPP PIM in the 12 months preceding follow-up (of these 30.1% had one and 26.9% had two or more PIMs) and the prevalence of START PPOs was 41.8% (with 29.2% having one PPO and 12.6% having multiple PPOs).[12] The most common STOPP criteria in the cohort were proton pump inhibitors at maximal dose for >8 weeks, aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event, and non-steroidal anti-inflammatory drugs (NSAIDs) with moderate to severe hypertension, while prevalent START omissions were calcium and vitamin D supplements in osteoporosis and anticoagulation in cases of atrial fibrillation or arrhythmia.[12] The percentage of individuals with both STOPP and START criteria was 24.8%.

In the 12 months preceding follow-up interview, 16.1% of participants reported one ED visit, 3.8% reported two visits and 1.8% reported three or more while 96.1% of participants reported visiting a GP (median 4 visits, interquartile range (IQR) 2.5-6). Results of the healthcare utilisation analysis are presented in Table 2. In the multivariate model for ED visits adjusted for covariates, presence of any STOPP PIM was significantly associated with higher rates of visits while the presence of a START PPO was not significantly associated. When number of criteria was considered, there was a statistically significant increase in the rate of ED visits for those with two or more STOPP criteria (adjusted IRR 1.42, 95% CI 1.06, 1.91) as well as for multiple START criteria (adjusted IRR 1.45, 95% CI 1.03, 2.04) relative to those with no criteria. For GP visits, having any STOPP PIM was associated with an increased rate of visits and having any PPO determined by START was not associated with a significant increase. In the model including number of criteria, the relationship of STOPP persisted

regardless of number of PIMs while two or more START PPOs were also significantly associated with increased GP visits (adjusted IRR 1.13, 95% CI 1.01, 1.27).

Difficulties with ADLs were reported by 7.7% of participants at baseline and 8.3% of participants reported an increase in ADLs which caused difficulty at follow-up. In the multivariate logistic regression analysis having any START PPO was significantly associated with functional decline, with a larger effect in the dose-response model for those with multiple criteria (adjusted OR 2.06, 95% CI 1.25, 3.39), however no evidence of an effect due to STOPP was found (Table 3). CASP-R12 scores at follow-up ranged from 5 to 36 (mean 26.2, SD 5.2). Multivariate linear regression found that neither presence of any STOPP nor any START criteria was significantly associated with CASP-R12 score (

Table 4). In Model 2, exposure to two or more START PPOs was associated with a small but statistically significant reduction in QoL (adjusted β coefficient -1.05, 95% CI -1.83, -0.26).

Variables for the interaction between STOPP and START showed no statistically significant association ($p > 0.05$) with any of the outcomes and likelihood ratio tests provided no evidence of improved model fit and therefore, interactions terms were not included. In the MSMs analysis weighted by the inverse probability of exposure to a STOPP PIM (binary), and the probability of censoring to account for loss to follow-up at Wave 2, the IRR for ED visits decreased in magnitude and became marginally non-significant (adjusted IRR 1.27, 95% CI 0.99, 1.64) and for GP visits the estimate also decreased slightly, but remained significant. For START, the adjusted odds ratio for functional decline increased slightly to 1.61 (95% CI 1.10, 2.34) in the MSM which may suggest a degree of confounding by indication by a time-dependent covariate. Results from the MSMs and standard analyses for each outcome are presented in Table S3.

Discussion

Older people in this study who were prescribed a STOPP PIM visited ED and their GP more often (for those with two or more PIMs, 42% and 16% increases in rate respectively), however no evidence of a relationship with functional decline and QoL was found. Participants with multiple PPOs had higher rates of healthcare utilisation (45% higher rate of ED visits and 13% more GP visits) and a small reduction in QoL. Having a START PPO was also associated with higher odds of functional decline over a two year period. Time-varying confounding did not appear to play a role in these associations.

Studies on the impact of PIP have predominantly used cross-sectional or retrospective cohort designs so this study is one of few to examine the prospective relationship between STOPP and START and patient outcomes.[7] One prospective study of older hospitalised patients found a significant association between STOPP and avoidable ADEs,[14] and this is supported by other work on ADEs.[15–18] For the outcomes examined in the present study, the findings appear to be consistent with previous research, in that the weight of evidence supports an association of STOPP with hospital visits,[16,19] while fewer studies have shown an effect of STOPP on health-related QoL,[16] vulnerability,[19] and functional decline during hospital stay,[17] and START on non-cardiovascular mortality.[20]

All studies that have applied STOPP and START together in the same study have been hospital based with limited research on older populations in the primary care setting. Secondary analysis of data from a trial of a hospital pharmacist intervention found the only significant association was between number of STOPP criteria and number of medication-related hospital readmissions,[21] and that both STOPP and START had poor discriminative ability to identify older patients at risk of unplanned rehospitalisation or death.[22] A study of patients following hip fracture showed higher all-cause mortality among patients with a greater combined number of STOPP and START criteria.[23] A case-control study of medication-related hospital admissions found an association with STOPP criteria and a composite of STOPP and START.[24] Studies that have used different measures of

inappropriate prescribing have also found an association with adverse outcomes in community-dwelling older people, such as the Medication Appropriateness Index and high-risk prescribing classified using the Drug Burden Index.[25,26] A recent trial in general practice targeting high-risk use of NSAIDs and antiplatelet drugs significantly reduced not only the targeted prescribing but also the rate of hospitalisations for related adverse events.[27]

Patients with either STOPP PIMs or START PPOs appear to have poorer outcomes, so incorporating review of these criteria into the care of older people and acting to rectify situations defined as inappropriate may benefit patients. When screening tools such as STOPP and START were developed, criteria were included if deemed by expert consensus to be potentially inappropriate with a marginally unfavourable risk-benefit ratio. This study provides evidence to support that this is the case and that there is an association between such prescribing and harm for patients. This is independent of the effect of number of medications, lending credence to the view that polypharmacy itself is not necessarily detrimental, but can be if it includes inappropriate prescribing.[28] However given the limited time available to healthcare professionals to review and optimise treatment, the modest size of the effect of PIP should be considered when prioritising issues to spend time on with patients. If reviewing PIP can be incorporated easily into routine clinical practice, for example through clinical decision support systems or by streamlining explicit measures to focus on fewer high-risk criteria, using these screening tools may be an efficient way to avoid extra healthcare utilisation, functional decline or reduced QoL. Further research should consider the cost-effectiveness of such approaches and large-scale prospective cohort studies or economic modelling would provide evidence to identify the most clinically significant prescribing issues to focus on in practice.

For patients who are identified as having PIP, discussing advantages and disadvantages of any medication change with the patient themselves is important. A recent trial in general practice to reduce PIP found that more changes were made when patients were present for medication

review.[29] Any discussion should put particular emphasis on the patient's own priorities as they may place different weights on various benefits and risks. This is especially important when considering starting a new medication to address a PPO, as it may be preferable to both prescriber and patient to not start a preventive treatment in advancing older age despite it being indicated.[30] Rigidly applying treatment guidelines can be ineffective as they do not take account of neither comorbidities nor patients' preferences and evidence often comes from trials which did not include older patients.[31,32] This is in contrast to the process of addressing PIMs which may require consideration of stopping a medicine.[33] Both types of PIP present distinct challenges and different approaches may be needed to address potential errors of commission and omission.[34]

Adjustment for time-dependent confounding using MSMs did not alter the results here, possibly because factors such as number of medicines were relatively time-stable over the study period. This may relate to therapeutic inertia, failure to start new drugs,[35] and conversely due to prescriber and patient reluctance to deprescribe treatments for fear of negative consequences.[36] Although MSMs may provide better evidence for causal relationships than conventional regression analyses, associations from longitudinal studies should also be interpreted in the context of other criteria for causation such as the Bradford Hill criteria.[37]

This is one of the first longitudinal studies in the community setting to determine the prospective relationship between PIP and adverse outcomes. This robust design allowed for baseline differences to be accounted for and also addressed a number of criteria for inference of causality in epidemiological studies, including temporality and biological gradient.[37] Pharmacy claims data as used here may provide more reliable determination of medication exposure compared to self-reported drug use.[38] However as dispensing data was used, it had to be assumed that dispensed medications were actually consumed and information on non-prescription medicines use was not available.

Limitations to the study were that a proportion of criteria from STOPP and START could not be applied to the data available in this study (see Table S1 for applicable criteria) and for those that were applied, this study did not have sufficient power to determine if any individual criteria were more strongly associated with adverse patient outcomes. The outcomes of healthcare utilisation and functional decline were patient reported rather than objective measures which may have affected accuracy, however the range of covariates adjusted for should have addressed any systematic reporting bias amongst participant subgroups.[39,40] The CASP-R12 is a measure of quality of life rather than health-related quality of life specifically and so may not have been sensitive to changes in the health status of participants. While this cohort was well characterised, there is still potential for the presence of unmeasured or unknown confounders. Although reverse causality could explain the relationships of START with adverse outcomes, i.e. preventive treatments being omitted in frailer patients with limited life expectancy who then experience functional decline and reduced QoL, controlling for baseline outcome differences and time-varying covariates should reduce this possibility.[8]

PIP determined by STOPP and START was associated with adverse outcomes in a prospective older community-dwelling cohort. If application of these criteria can be integrated into routine medication review, they may help to support prescribers in optimising treatment and improve patient outcomes. Although such prescribing is only potentially inappropriate, the independent effects identified add weight to the suggestion that PIP is a marker of healthcare quality and patient safety and should be minimised if possible.

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Contributors: All authors conceived and designed this study. Data was acquired by KB (HSE-PCRS) and RAK (TILDA). FM carried out the statistical analysis and all authors interpreted the data. The manuscript was drafted by FM and all authors were involved in the critical revision of this and approval of the final manuscript.

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Figures

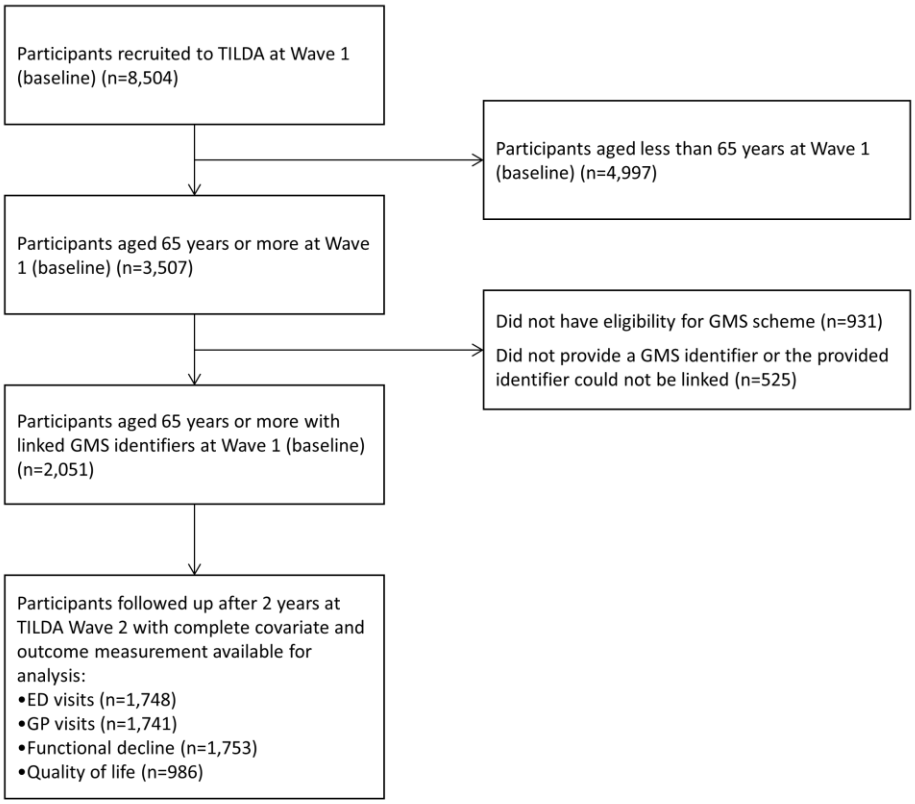

Figure 1 Flow diagram of study participants The Irish Longitudinal Study on Ageing (TILDA).

Tables

Table 1 Descriptive statistics for participants at baseline (Wave 1) and follow-up (Wave 2).

	Baseline (Wave 1) (n=2051)	Follow-up (Wave 2) (n=1753)
Age (years, mean (SD))	74.8 (6.17)	76.5 (6.04)
Age group (years, n (%))		
65-74	1087 (53.0)	754 (43.0)
≥ 75	964 (47.0)	999 (57.0)
Sex (Female, n (%))	1107 (54.0)	953 (54.4)
Number of repeat drug classes (median (IQR))	5 (3-8)	6 (3-9)
Number of reported conditions (n (%))		
0	214 (10.4)	88 (5.0)
1	423 (20.6)	268 (15.3)
2	498 (24.3)	370 (21.1)
3 or more	916 (44.7)	1027 (58.6)
Level of education attainment (n (%))		
None/primary	1056 (51.5)	879 (50.2)
Secondary	642 (31.3)	565 (32.3)
Third/higher	351 (17.1)	308 (17.6)
Living arrangements (n (%))		
Living alone	718 (35.0)	626 (30.5)
Living with spouse	965 (47.1)	793 (38.7)
Living with others	368 (17.9)	632 (30.8)
Private health insurance (n (%))	891 (43.4)	760 (43.4)
Diagnosed mental health condition (n (%))	129 (6.3)	157 (9.0)
Any hospital admission (n (%))	354 (17.3)	366 (20.9)
Moderate activity (n (%))	799 (39.0)	751 (42.8)
Depressive symptoms (n (%))*		
None	1172 (58.2)	1248 (74.9)
Sub-clinical	613 (30.4)	277 (16.6)
Clinical	230 (11.4)	141 (8.5)
Social participation (n (%))	943 (46.0)	826 (47.1)

*Depressive symptoms measured by Centre for Epidemiological Studies Depression scale missing for 36 participants at baseline and 87 participants at follow-up.

Table 2 Number (percentage) with an emergency department (ED) visit and mean (standard deviation) GP visits the 12 months preceding follow-up by subgroup and adjusted incident rate ratios (95% CI) for ED visits (n=1,748) and GP visits (n=1,741)

		Emergency department visits	
	n (%)	Adjusted IRR (95% CI)[a]	
		Model 1[b]	Model 2[c]
Any STOPP PIM (vs none)	246 (25.6)	1.30 (1.02, 1.66)*	-
Number of STOPP PIMs			
0 (reference)	134 (17.0)		
1	121 (22.4)	-	1.23 (0.94, 1.62)
≥2	125 (29.6)	-	1.42 (1.06, 1.91)*
Any START PPO (vs none)	174 (26.1)	1.23 (0.98, 1.53)	-
Number of START PPOs			
0 (reference)	206 (19.0)		
1	118 (24.3)	-	1.15 (0.90, 1.46)
≥2	56 (30.9)	-	1.45 (1.03, 2.04)*
		GP visits	
	Mean (SD)	Adjusted IRR (95% CI)[a]	
		Model 1[b]	Model 2[c]
Any STOPP PIM (vs none)	6.3 (6.4)	1.15 (1.06, 1.24)*	-
Number of STOPP PIMs			
0 (reference)	4.5 (4.9)		
1	5.9 (6.3)	-	1.14 (1.05, 1.25)*
≥2	6.8 (6.6)	-	1.16 (1.06, 1.28)*
Any START PPO (vs none)	5.9 (6.1)	1.04 (0.97, 1.12)	-
Number of START PPOs			
0 (reference)	5.2 (5.7)		
1	5.6 (5.8)	-	1.01 (0.93, 1.09)
≥2	6.9 (6.6)	-	1.13 (1.01, 1.27)*

[a] Adjusted for age group, gender, number of repeat drug classes, number of reported conditions, level of educational attainment, living arrangements, private health insurance status and number of ED/GP visits reported at baseline

[b] PIP exposure assessed using binary variables for presence or absence of STOPP and START

[c] PIP exposure assessed using categorical variables for presence of 0, 1 and ≥2 STOPP and START criteria

* $p < 0.05$

Table 3 Number (percentage) with an increase in ADL difficulties (functional decline) between baseline and follow-up by subgroup and adjusted odds ratios (95% CI) for functional decline compared to no functional decline (n=1,753)

	n (%)	Functional decline Adjusted OR (95% CI)[a]	
		Model 1[b]	Model 2[c]
Any STOPP PIM (vs none)	110 (11.0)	1.23 (0.78, 1.92)	-
Number of STOPP PIMs			
0 (reference)	35 (4.6)		
1	45 (8.5)	-	1.23 (0.75, 2.02)
≥2	65 (13.8)	-	1.25 (0.75, 2.06)
Any START PPO (vs none)	84 (11.5)	1.55 (1.07, 2.25)[d]	-
Number of START PPOs			
0 (reference)	61 (6.0)		
1	50 (9.8)	-	1.35 (0.89, 2.04)
≥2	34 (15.4)	-	2.06 (1.25, 3.39)[d]

[a] Adjusted for age group, gender, number of repeat drug classes, number of reported conditions, level of educational attainment, living arrangements, reporting diagnosis of a mental health conditions, reporting a hospital admission in the 12 months preceding follow-up and reporting moderate activity at baseline

[b] PIP exposure assessed using binary variables for presence or absence of STOPP and START

[c] PIP exposure assessed using categorical variables for presence of 0, 1 and ≥2 STOPP and START criteria

* $p < 0.05$

Table 4 Mean (standard deviation) of CASP-R12 quality of life score at follow-up by subgroup and adjusted β coefficient (95% CI) for CASP-R12 score (n=986)

	Mean (SD)	CASP-R12 score Adjusted β coefficient (95% CI)[a]	
		Model 1[b]	Model 2[c]
Any STOPP PIM (vs none)	25.5 (5.4)	-0.26 (-0.81, 0.29)	-
Number of STOPP PIMs			
0 (reference)	27.0 (5.0)		
1	26.2 (5.1)	-	-0.21 (-0.81, 0.39)
≥2	24.7 (5.5)	-	-0.45 (-1.16, 0.27)
Any START PPO (vs none)	25.5 (5.4)	-0.24 (-0.75, 0.26)	-
Number of START PPOs			
0 (reference)	26.7 (5.1)		
1	26.0 (5.2)	-	0.08 (-0.48, 0.64)
≥2	24.2 (5.7)	-	-1.06 (-1.84, -0.27)*

[a] Adjusted for age group, gender, number of repeat drug classes, number of reported conditions, level of educational attainment, living arrangements, level of depressive symptoms, reporting social participation and CASP-R12 score at Baseline

[b] PIP exposure assessed using binary variables for presence or absence of STOPP and START

[c] PIP exposure assessed using categorical variables for presence of 0, 1 and ≥2 STOPP and START criteria

* $p < 0.05$

Supporting material

Table S1 List of applicable criteria from STOPP and START used to determine exposure to PIMs and PPOs

Physiological system	Criteria
STOPP	
Cardiovascular	Digoxin at dose >125 µg/day
	Loop diuretic for dependent ankle oedema only
	Loop diuretic as first-line monotherapy for hypertension
	Thiazide diuretic with a history of gout
	Non-cardioselective β blocker with COPD
	β blocker in combination with verapamil
	Aspirin and warfarin in combination without histamine H_2 receptor antagonist (except Cimetidine) or PPI
	Dipyridamole as monotherapy for cardiovascular secondary prevention
	Aspirin with history of PUD without H_2 receptor antagonist or PPI
	Aspirin at dose >150 mg/day
	Aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event
CNS	TCAs with dementia
	TCAs with glaucoma
	TCAs with cardiac conductive abnormalities
	TCAs with an opiate or calcium channel blocker
	Long-term (>1 month), long-acting benzodiazepines
	Long-term (>1 month) neuroleptics
	Long-term (>1 month) neuroleptics in those with Parkinsonism
	Phenothiazines in patients with epilepsy
	Anticholinergics to treat extrapyramidal side-effects of neuroleptics
	Prolonged use (>1 week) of first generation antihistamines
Gastrointestinal	Prochlorperazine or metoclopramide with Parkinsonism
	PPI at full therapeutic dosage for >8 weeks
Respiratory	Theophylline as monotherapy for COPD
	Systemic corticosteroids instead of inhaled corticosteroids in COPD
	Nebulised ipratropium with glaucoma
Musculoskeletal	NSAID with history of PUD, unless with concurrent H_2 receptor antagonist, PPI or misoprostol
	NSAID with moderate-severe hypertension >160/100 mmHg[a]
	NSAID with heart failure
	Long-term use of NSAID (>3 months)
	Warfarin and NSAID together
	NSAID with chronic renal failure
	Long-term corticosteroids (>3 months) as monotherapy for rheumatoid

Physiological system	Criteria
	arthrtitis/osteorarthritis
Urogenital	Bladder antimuscarinic drugs with dementia
	Bladder antimuscarinic drugs with chronic glaucoma
	α blockers in males with frequent incontinence
Endocrine	Glibenclamide or chlorpropamide with type 2 diabetes mellitus
	Oestrogens with a history of breast cancer
Falls risk	Benzodiazepines in those prone to falls
	Neuroleptic drugs in those prone to falls
	First generation antihistamines in those prone to falls
	Long-term opiates (>1 month) in those with recurrent falls
Analgesia	Use of long-term strong opiates as first line therapy for mild-moderate pain
	Regular opiates for >2 weeks without concurrent use of laxatives
Duplicates	Any regular duplicate drug class prescription e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors, or other antidepressant
START	
Cardiovascular	Warfarin (or another oral anticoagulant) in the presence of chronic atrial fibrillation
	Aspirin/clopidogrel with a history of atherosclerotic coronary, cerebral or peripheral vascular disease
	Antihypertensive therapy where systolic blood pressure >160 mmHg[a]
	Statin therapy with a history of coronary, cerebral or peripheral vascular disease
	ACE inhibitor with chronic heart failure
	ACE inhibitor following acute myocardial infarction
	β blocker with chronic stable angina
Respiratory	Regular inhaled β_2 agonist or anticholinergic agent for mild to moderate asthma or COPD
CNS	L-DOPA in Parkinson's with definite functional impairment
	Antidepressant drug in the presence of moderate-severe depressive symptoms
Musculoskeletal	Bisphosphonates if taking oral corticosteroids for >3 months
	Calcium and vitamin D supplement with osteoporosis
Endocrine	ACE inhibitor or ARB in diabetes with nephropathy
	Antiplatelet therapy in diabetes mellitus if ≥1 major CV risk factor (hypertension, hypercholesterolaemia, smoking history)
	Statin therapy in diabetes mellitus if ≥1 major CV risk factor

Abbreviations: ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blocker, COPD: chronic obstructive pulmonary disease, CV: cardiovascular, NSAID: non-steroidal anti-inflammatory drug, PPI: proton pump inhibitor, PUD: peptic ulcer disease, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant

[a] Hypertension defined using objectively measured blood pressure or self-reported hypertension diagnosis with antihypertensive medication

Table S2 Description of covariates adjusted for in multivariate regression models

Variable	Format	Description of categories
• Age group	Binary	65-74 years (reference) ≥ 75 years
• Gender	Binary	Male (reference) Female
• Number of repeat drug classes[a]	Continuous	N/A
• Number of reported conditions[b]	Categorical	0 (reference) 1 2 3 or more
• Level of education attainment	Categorical	None/primary (reference) Secondary Third/higher
• Living arrangements	Categorical	Living alone (reference) Living with spouse Living with others
• Private health insurance	Binary	No (reference) Yes
• Number of ED visits at baseline	Continuous	N/A
• Number of GP visits at baseline	Continuous	N/A
• Diagnosed mental health condition[c]	Binary	No (reference) Yes
• Any hospital admission in 12 months pre follow-up	Binary	No (reference) Yes
• Moderate physical activity at baseline	Binary	No (reference) Yes
• Depressive symptoms[d]	Categorical	None (reference) Sub-clinical Clinical
• Social participation[e]	Binary	No (reference) Yes
• CASP-R12 score at baseline	Continuous	N/A

[a] Number of medicines (defined by level 3 ATC code) dispensed in at least 3 months to a participant during the 12 months of PIP exposure measurement in HSE-PCRS (with an upper bound of 10 or more medicines).

[b] The number of doctor-diagnosed chronic conditions reported by the participants at the TILDA interview from the following list: cardiovascular disease (heart attack, heart failure or angina), cataracts, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer, and hip fracture.

[c] Reported a doctor-diagnosed emotional, nervous or psychiatric problem during TILDA interview

[d] Level of symptoms screened by the Centre for Epidemiological Studies Depression scale (CES-D) in the self-completion questionnaire at follow-up. None corresponds to a CES-D score of 0-7, sub-clinical to a score of 8-15, and clinical to a score of >15.

[e] Reported social participation in any groups such as sports or social groups

Table S3 Comparison of adjusted parameter estimates (95% CI) for presence of any STOPP PIM and any START PPO from unweighted multivariate regression models and marginal structural (weighted) models

	Unweighted analysis	p	Weighted analysis (MSM)[a]	p
STOPP				
ED visits (IRR (95% CI))	1.31 (1.02, 1.67)	0.031	1.27 (0.99, 1.64)	0.063
GP visits (IRR (95% CI))	1.15 (1.06, 1.24)	0.001	1.15 (1.06, 1.25)	0.001
Functional decline (OR (95% CI))	1.21 (0.77, 1.89)	0.411	1.19 (0.71, 2.01)	0.499
CASP-R12 score (β coeff (95% CI))	-0.26 (-0.81, 0.29)	0.353	-0.31 (-0.92, 0.30)	0.322
START				
ED visits (IRR (95% CI))	1.24 (0.99, 1.54)	0.063	1.26 (0.99, 1.60)	0.062
GP visits (IRR (95% CI))	1.04 (0.97, 1.12)	0.288	1.04 (0.95, 1.14)	0.406
Functional decline (OR (95% CI))	1.54 (1.06, 2.24)	0.024	1.61 (1.1, 2.34)	0.014
CASP-R12 score (β coeff (95% CI))	-0.25 (-0.76, 0.26)	0.34	-0.05 (-0.58, 0.50)	0.858

[a] Weighted by product of stabilised inverse probability of exposure and probability of remaining uncensored at follow-up