Potentially inappropriate prescribing among people with dementia in primary care: a retrospective cross-sectional study using the Enhanced Prescribing Database

Running title

Potentially inappropriate prescribing in dementia

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Abstract

Background Little is known about prescribing appropriateness for community-dwelling people with dementia (PWD).

Objective To estimate potentially inappropriate prescribing (PIP) prevalence among PWD in primary care in Northern Ireland, and to investigate associations between PIP and polypharmacy, age and gender.

Methods A retrospective cross-sectional study was conducted, using data from the Enhanced Prescribing Database. Patients were eligible if a medicine indicated for dementia management was dispensed to them during 01/01/2013 – 31/12/2013. Polypharmacy was indicated by use of ≥4 repeat medications from different drug groups. A subset of the Screening Tool of Older Persons Potentially Inappropriate Prescriptions (STOPP) criteria, comprising 36 indicators, was applied to the dataset. Overall prevalence of PIP and the prevalence per each STOPP criterion was calculated as a proportion of all eligible persons in the dataset. Logistic regression was used to investigate associations between PIP, polypharmacy, age and gender.

Results The study population comprised 6826 patients. Polypharmacy was observed in 81.5% (*n*=5564) of patients. PIP prevalence during the study period was 64.4% (95% CI 63.2 – 65.5*;* *n*=4393). The most common instance of PIP was the use of anticholinergic/antimuscarinic medications (*n*=1718; 25.2%; 95% CI 24.2 – 26.2). In multivariable analyses, both polypharmacy and gender (being female) were associated with PIP, with odds ratios of 7.6 (95% CI 6.6 – 8.7) and 1.3 (95% CI 1.2 – 1.4) respectively. No association was observed between PIP and age, after adjustments for gender and polypharmacy.

Conclusion This study identified a high prevalence of PIP in community-dwelling PWD. Future interventions may need to focus on certain therapeutic categories and polypharmacy.

Keywords: Dementia; pharmacoepidemiology; inappropriate prescribing; polypharmacy; primary health care

INTRODUCTION

Demographic ageing is a process taking place worldwide, and is reflective of the major advancements in healthcare over the last century. Consequently, prescribing for older people, conventionally defined as those aged 65 years and over, is becoming an increasingly important aspect of clinical care, and one that requires prudent consideration from prescribers [1]. The presence, and subsequent management of, multiple morbidities in older patients will often result in polypharmacy [2], which has frequently been described as the concurrent use of four or more medications [3, 4]. Use of ten or more medications has been termed 'excessive polypharmacy' [5]. While polypharmacy may be appropriate and therapeutically beneficial where a number of medications are clinically indicated (such as patients with complex or multiple conditions) [2], it is known to be a risk factor for adverse drug events (ADEs), drug-drug and drug-disease interactions, and potentially inappropriate prescribing (PIP) [3, 4, 6]. PIP refers to the use of medicines that introduce a greater risk of adverse drug-related events where a safer, as effective alternative is available to treat the same condition [6]. PIP is associated with increases in negative outcomes such as morbidity, ADEs, hospitalisations and mortality [7, 8], and is reported to be common amongst older people [9-11]. A myriad of tools have been developed to identify inappropriate prescribing [2, 7]. The recently updated Screening Tool of Older Person's Prescriptions (STOPP) criteria is a screening tool comprising 80 clinically significant criteria for PIP in older people, primarily organised by physiological system, validated by a Europe-wide Delphi consensus panel [12]. These evidence-based criteria take drug-drug and drug-disease interactions, drug doses, duration of treatment, and clinical effectiveness into consideration when determining the appropriateness of the prescribed treatments. Each criterion is accompanied by a concise, evidence-based explanation as to why the prescribing practice is potentially inappropriate. The STOPP criteria have been extensively validated for use in the United Kingdom (UK) setting [2].

Consideration of the appropriateness of prescribing for people with dementia (PWD) is particularly important due to the unique medication needs that this vulnerable population have in comparison to the rest of the older population. The presence of other comorbidities and complex medication regimens with possible psychoactive drug use, together with deficits in cognition and communication and diminishing decision-making capacity, generate challenges with medication management, particularly adherence [13]. Such issues may also influence doctors' prescribing behaviour and the quality of chronic illness management [14, 15]. For example, Wood-Mitchell *et al*. reported that psychiatrists in England felt under pressure to prescribe for PWD experiencing behavioural and psychological symptoms and did not always adopt an evidence-based approach to

prescribing activity [13]. Whilst a number of studies have reported on appropriateness of prescribing for PWD, these tend to focus on dementia patients living in long-term care facilities [16, 17], those at the end of life [18, 19], or those prescribed antipsychotic medications [20, 21]. Less attention has been paid to PWD living in their own homes within the primary healthcare setting. Studies that have specifically investigated inappropriate medication use within this dementia patient population have been small in size and relied on patient or caregiver reports of drug use [22-26].

An assessment of the appropriateness of prescribing for PWD, especially those managed within the primary healthcare setting, may help to identify a population likely to benefit from interventions to optimise prescribing practices. Therefore, the aim of this pharmacoepidemiological study was to estimate the prevalence of PIP among PWD in primary care in Northern Ireland (NI), by applying a subset of the STOPP criteria to a prescribing database. We also sought to explore the association between PIP and factors such as polypharmacy, age and gender, to more precisely characterise those with dementia who might be at risk of PIP.

MATERIALS AND METHODS

Setting

Northern Ireland is part of the UK, has a population of ~1.7 million, and primary healthcare is delivered through ~330 general practices. Healthcare in NI is provided under the UK's National Health Service (NHS), where health and social care is publicly funded through central taxation and is free-of-charge at the point of need to all citizens. Unlike some other countries in the UK (namely England and Scotland), prescriptions (and therefore all medications) have been free in NI since prescription charges were phased out in 2010.

Data source

Data were extracted from the Enhanced Prescribing Database (EPD), which securely holds information on drugs prescribed and subsequently dispensed to patients in primary care in NI. The EPD does not contain data relating to prescribing in the hospital setting or over-the-counter (OTC) medication use. Once prescriptions have been dispensed by community pharmacies, they are forwarded to the Health and Social Care (HSC) Business Services Organisation (BSO) at the end of each month for reimbursement. Computer-generated prescriptions contain a unique two-dimensional barcode which is scanned by the BSO during the reimbursement process. This barcode links a patient's Health and Social Care Number with details of their prescribed medication and prescriber. Once this information is scanned by the BSO, it is held in a secure database, the EPD. At

present, approximately 85-90% of all prescriptions forwarded to the BSO result in data of research standard, which has helped to generate a central database of approximately 1.9 million patients in NI [9]. Diagnoses and other clinical information are not recorded in the EPD.

Study design and population

This was a retrospective, cross-sectional study using data from the EPD. Ethical approval was received from the NHS Research Ethics Committee London – City Road and Hampstead (14/LO/1891). Study participants were identified by a computerised search of the EPD, which was conducted by BSO data custodians. The study population comprised all individuals in the EPD who were dispensed a drug for the management of dementia (donepezil, galantamine, rivastigmine, memantine) during the study period 01/01/2013 – 31/12/2013. These drugs were used as proxy measures for diagnosis of dementia in the absence of clinical information about individuals. Patients in the EPD who entered a care home on or before 31/12/2013 were excluded, as were patients who left NI or died during the study period. In order to apply certain STOPP criteria, all patients were required to have at least three months of lead-in data prior to 01/01/2013, to ascertain long-term use of certain medications. All data were anonymised and the research team had no access to any patient identifiable data.

The final version of the dataset that was available to the research team included a unique patient identifier and information on patients' age (in years), gender, the month and year in which a prescription was scanned by the BSO, and data on all items prescribed (such as the drug name, strength, quantity, and date of issue) during the study period.

Exposures

Thirty-eight of the 80 STOPP indicators were deemed suitable by the research team for application to the EPD dataset in the absence of clinical or diagnostic information. Some indicators could not be applied due to the absence of clinical or diagnostic data and were therefore excluded. For example, '*aldosterone antagonists with concurrent potassium-conserving drugs without monitoring of serum potassium*' could not be operationalised due to the absence of data on biochemical monitoring, and therefore, was not included. For some criteria, prescription drugs for the treatment of certain disease conditions were identified in the EPD dataset and used as proxies for diagnosis, where possible, such as for glaucoma and gout (Supplementary table 1). This method has been used in other studies [8, 9]. During analysis, the following two STOPP indicators were unable to be operationalised due to lack of long-term prescribing data: *'long-term use of NSAID for symptom relief*

of osteoarthritis where paracetamol has already been tried' and '*long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor*'. Therefore, a total of 36 STOPP indicators were applied to the final dataset.

Data on drug use were extracted using British National Formulary (a standard drug reference text used in the UK) codes [1]. Patients were categorised into those who received a STOPP criteria drug or drug combination. STOPP criteria which specified a particular duration, such as '*benzodiazepines for ≥4 weeks*', were assessed by identifying individuals who used the drugs for durations exceeding these 'appropriate' thresholds within the study period (using the month a prescription was scanned by the BSO). STOPP criteria which specified a particular dosage not to be exceeded, such as '*oral elemental iron doses greater than 200mg daily*', were evaluated by calculating the number of daily defined doses (DDDs) for each recipient using the strength and quantity of the dispensed medication for each prescription.

The total number of prescriptions dispensed for each different drug group (according to BNF code) was calculated for each individual, during the one year study period. A 'repeat medication' was defined as one for which the patient received three or more prescriptions for that agent in the study period. Polypharmacy was examined by the use of four or more repeat medications from different drug groups.

Outcomes

The primary outcome was the overall prevalence of PIP in PWD in primary care in NI in 2013, according to a subset of the STOPP criteria. Secondary outcomes measures were: (i) the prevalence of PIP per individual STOPP criterion, and (ii) the association between PIP and polypharmacy, gender, and age group.

Statistical analysis

The overall prevalence of PIP in the study population and the prevalence per individual STOPP criterion in 2013 (the study period) were calculated as a proportion of all eligible persons in the dataset, and reported as percentage estimate and 95% confidence intervals (CI). Adjusted logistic regression analyses were used to calculate odds ratios (OR) and 95% CI to investigate the association between any (versus no) PIP and polypharmacy (categorised as 0-3 versus ≥4 repeat drug classes), age group (≤44, 45-64, 65-84, ≥85 years) and gender (male, female). There were no missing data for

the variables of interest. Analyses were performed using STATA SE v13 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of the study population

For the study period, 6826 persons identified in the EPD were eligible for inclusion in the study (Table 1). Of these, approximately two-thirds were female (*n*=4393, 64.4%), with a mean age of 79.6 [standard deviation (SD) ±8.0] years. Patients were taking a mean number of 6.8 (SD ±3.5) repeat medications. Over three-quarters of patients (*n*=5564, 81.5%) were receiving four or more repeat medications (the definition of polypharmacy adopted for this study), whilst the use of ten or more repeat medications was observed in one-fifth of patients (*n*=1427, 20.9%).

[Insert Table 1 here]

Overall prevalence of PIP in 2013

The overall prevalence of PIP in the study period, according to the 36 STOPP indicators that were applied to the dataset, was 64.4% (95% CI 63.2 – 65.5) (*n*=4393). Over one-fifth of the population [*n*=1571, 23.0% (95% CI 22.0 – 24.0)] was prescribed one potentially inappropriate medication, 1141 patients [16.7% (95% CI 15.8 – 17.6)] were prescribed two potentially inappropriate medications, and 1681 patients [24.6% (95% CI 23.6 – 25.7)] were prescribed three potentially inappropriate medications.

Prevalence of PIP in 2013 according to individual STOPP criteria

Table 2 describes the prevalence for each STOPP criterion. The most common instance of PIP was the use of anticholinergic/antimuscarinic medications (*n*=1718, 25.2%). The second most frequently prescribed potentially inappropriate medicines were proton pump inhibitors (PPIs) at full therapeutic dosage for >8 weeks (*n*=1561, 22.9%), followed by acetylcholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate (*n*=1276, 18.7%), benzodiazepines for ≥4 weeks (*n*=777, 11.4%), and use of regular opioids without concomitant laxative (*n*=715, 10.5%). Duplication of therapy within drug classes was most frequently observed with opioid analgesics (*n*=346, 5.1%) and benzodiazepines (*n*=239, 3.5%). Many other STOPP criteria had a prevalence less than 1.0%, such as '*thiazide diuretic with a history of gout*' and '*phenothiazines as first-line treatment, since safer and more efficacious alternatives exist*'.

[Insert Table 2 here]

Factors associated with PIP

Univariate logistic regression confirmed that polypharmacy, age and gender were significantly associated with PIP (Table 3). A strong association between PIP and polypharmacy was observed. Those receiving four or more repeat medications were seven and a half times more likely to be exposed to PIP compared to those on zero to three repeat medications (adjusted OR 7.6, 95% CI 6.6 – 8.7). PIP was more likely to occur in females than in males after adjusting for age and polypharmacy (adjusted OR 1.3, 95% CI 1.2 – 1.4). No association was observed between PIP and age after adjustments for gender and polypharmacy.

[Insert Table 3 here]

DISCUSSION

Findings

Based on the data from a comprehensive dispensing database of 6826 dementia patients in NI, we found that both polypharmacy and PIP were prevalent among this community-dwelling patient population during 2013. PIP occurred in nearly two-thirds of the population (64.4%), according to the subset of STOPP criteria applied. The most commonly prescribed potentially inappropriate medicines were anticholinergic/antimuscarinic medications, followed by PPIs at maximum therapeutic dosage for >8 weeks, acetylcholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate, and benzodiazepines for ≥4 weeks. Polypharmacy and gender were significantly associated with PIP. Age was not associated with PIP.

To our knowledge, this is one of the first studies to apply the STOPP criteria to a large prescribing database in order to ascertain the prevalence of PIP amongst community-dwelling dementia patients. Previous studies have reported a lower prevalence of potentially inappropriate medication use (between 15% and 47%) among community-dwelling dementia patients, as reported using either the Beers criteria or PRISCUS list (a tool developed for use in Germany) [22-26]. The prevalence of PIP in our study was nearly double that reported by Bradley *et al*. who investigated PIP in older people (aged ≥70 years) in NI using the STOPP criteria, but whose methodology did not focus specifically on PWD [10].

In addition, we found that the prevalence of polypharmacy, as defined by the use of four or more repeat medications, was high amongst this patient population (81.5%). Again, this is difficult to directly compare with previous studies which have used different numeric thresholds to define polypharmacy in their study populations. However, this finding is much greater than that reported by Montastruc *et al*. [26] and Lau *et al*. [23] who reported polypharmacy (≥5 medications) in 43% and 52% respectively of community-dwelling patients with dementia. A high prevalence of polypharmacy is unsurprising in PWD, as often this patient population will suffer from a number of comorbidities due to their increasing age and frailty [27]. Whilst patients in the current study population ranged in age from 34 to 100 years, they had a mean age of 79.6 years, and would therefore be expected to be receiving a number of different medications for comorbid conditions. There has been discussion within the literature about reducing reliance on numeric thresholds for polypharmacy and considering instead the appropriateness of polypharmacy, taking into account the fact that the use of 'many drugs' may be necessary for those with multimorbidities [2, 28].

This study revealed a number of instances of PIP; some of these, such as the use of PPIs at full therapeutic dosage for >8 weeks and benzodiazepines for ≥4 weeks, are unsurprising and are consistent with findings reported in other studies exploring PIP amongst older people [10, 11] and PWD in care homes [17]. The prescribing of anticholinergic/antimuscarinic medications in our study population, received by one-quarter of patients (25.2%), was a concerning finding. The use of these drugs in PWD is not recommended due to their association with decline in both physical and cognitive function [29], and yet other studies have found similarly prevalent use of anticholinergics in dementia patients [24, 26, 30]. A number of tools have been developed to measure the anticholinergic drug burden, such as the validated Anticholinergic Cognitive Burden Scale [31]. The availability of such tools to clinicians could prove invaluable during an in-depth medication review with dementia patients, and may help them to change patients to alternative drugs with a lower anticholinergic burden. In some situations, non-pharmacological measures could be used as alternatives to prescribing anticholinergic medications, for example scheduling regular toilet breaks and making dietary modifications instead of using bladder antispasmodics [32].

Practice implications

In our study, the high prevalence of both polypharmacy and PIP could serve as an indicator that review of these patients is required to fully assess the appropriateness of the medication regimens used, particularly considering the strong relationship we observed between polypharmacy and PIP, which has been reported previously [9-11, 17, 22-23, 25-26]. This study also revealed that PIP among

community-dwelling dementia patients was associated with female gender, but not age. Again, these relationships have been reported elsewhere [9-11, 25-26] and would be of assistance to clinicians identifying patients at risk of PIP. These associations may be useful in generating hypotheses which could be explored in other datasets. Consideration of PIP, polypharmacy and gender could be incorporated into clinicians' prescribing systems in order to alert them to such high-risk patients and potentially inappropriate medication combinations [33]. Medication review is just one component of medicines optimisation, employing a patient-focused and person-centred approach which ensures that patients obtain the best possible outcomes from their medicines [34]. Often GPs find it difficult to incorporate robust medication review into consultations due to time constraints; opportunity therefore exists for other healthcare professionals such as community pharmacists and nurses to assist with this and examples of such interventions in a primary care setting have been reported in the literature [35-37]. With respect to pharmacists, the role of the GP practice-based pharmacist is expanding and a pilot scheme will be launched in the UK during 2016 [38]. These pharmacists will be ideally placed to assist with medication review of patients and will also be able to identify patients at high risk from PIP and potentially inappropriate medications.

Deprescribing is another way in which inappropriate medication use and polypharmacy may be managed [39], and could prove to be a useful intervention in this particular patient population. For example, 'drug holidays' (where medication is stopped for a trial period to assess effectiveness of treatment and/or remission of symptoms [40]) could be advocated for anticholinergic medications, such as those for urinary incontinence. Deprescribing is an emerging area within the scientific literature and it has been acknowledged that a wider evidence-base is needed to support such an approach [41-44]. It has been reported that deprescribing may be particularly complicated in PWD due to their diminishing capacity and involvement in decision-making about their medicines, and difficulties with communication and understanding [45]. Reeve *et al*. have called for further research into the beliefs and preferences of dementia patients and their carers in order to better understand how deprescribing can be of optimal benefit to this patient population [45].

Strengths and limitations

This is one of the largest epidemiological studies to use a prescription-based database to estimate PIP amongst community-dwelling dementia patients. The EPD holds information on all prescriptions dispensed in community pharmacies in NI, and the high scan rate of prescriptions has generated a reliable database of great use to researchers. Although we have confidence in the generalisability of the results to the wider dementia patient population within NI, there are a number of

methodological limitations which may limit generalisability of the findings to other settings. The lack of clinical information within the EPD, notably diagnostic data, means there could be an underestimation of the prevalence of patients with dementia. We had to identify patients who had received one of four drugs used in the management of dementia, using these medications as a proxy for a dementia diagnosis. These drugs are licensed for the treatment of mild to moderate dementia in Alzheimer's disease (donepezil, galantamine), moderate to severe dementia in Alzheimer's disease (memantine) or mild to moderate dementia in Parkinson's disease (rivastigmine) [1]. Whilst this may have excluded those with dementia of different aetiologies or those with severe cases in whom the medication had been stopped, we had no alternative means of identifying the patient population for inclusion in the study in the absence of diagnostic information. In addition, the lack of clinical data within the EPD only allowed us to apply a subset of the STOPP criteria and some diagnoses had to be determined using drug proxies, an analytical approach which has been used previously [9, 10, 46]. Therefore some instances of PIP identified within this study may not be clinically relevant, and clinicians must ensure that prescribing decisions are also based upon their clinical and personal knowledge of each patient. A set of explicit prescribing criteria for dementia is under development in Australia [47] and may be useful to researchers carrying out similar epidemiological studies in the future. The EPD was chosen for its relevance to the NI setting over other databases such as the Clinical Practice Research Datalink (CPRD), which is not representative of NI prescribing data [48]. Other limitations of using drug dispensing data is that patient adherence to medication is assumed. Use of over-the-counter (OTC) medications purchased without a prescription is not accounted for, which may under-estimate or over-estimate PIP prevalence and use of anticholinergic/antimuscarinic medications in particular, due to the anticholinergic effect of many OTC sleeping aids and antihistamines.

Despite these limitations, polypharmacy and PIP are prevalent among community-dwelling dementia populations; female patients and those receiving four or more medications may be at particular risk from inappropriate prescribing practices. This study has added to the limited body of epidemiological work undertaken with the community-dwelling dementia population as its focus, and may assist clinicians to identify 'at-risk' dementia patients in need of medication review within the primary care setting. Further pharmacological studies should be undertaken to validate the findings from the present study in other settings, such as the rest of the UK or Europe. Future work should also focus on exploring GPs' prescribing behaviours for these patients to further understand the factors influencing prescribing decisions.

ACKNOWLEDGEMENTS

The authors wish to thank the staff at the HSC Business Services Organisation, Information and Registration Unit for supplying data from the Enhanced Prescribing Database and providing technical support throughout the study. This work was funded by the HSC Research & Development Division of the Public Health Agency in Northern Ireland and The Atlantic Philanthropies (Ref: COM/5020/14). The funders had no role in the design or conduct of the study; in the analysis and interpretation of the data; or in the preparation or approval of the manuscript.

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TABLES

Table 1. Characteristics of the study population in the Enhanced Prescribing Database (EPD) dataset (*n*=6826)

Variables	Prevalence, *n* (%)	Mean (±SD)	Range
Gender			
Male	2433 (35.6)		
Female	4393 (64.4)		
Age (years)		79.6 (8.0)	34 – 100
≤44	7 (0.1)		
45-64	275 (4.0)		
65-84	4582 (67.1)		
≥85	1962 (28.7)		
Number of repeat medications		6.8 (3.5)	1 – 23
Polypharmacy (≥4 medications)			
Never	1262 (18.5)		
Ever	5564 (81.5)		

Table 2. Prevalence of potentially inappropriate prescribing in 2013 among 6826 people with dementia in Northern Ireland by individual STOPP criteria

Criteria description (potential risk)	Number of patients	% of patients (95% CI)
Indication of medication		
Any drug prescribed beyond the recommended duration, where treatment duration is well defined		
Zopiclone and zolpidem (up to 4 weeks)	573	8.4 (7.8 – 9.1)
NSAIDs (up to 3 months)	124	1.8 (1.6 – 2.2)
Any duplicate drug class prescription *(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent)*		
Opioid analgesics	346	5.1 (4.6 – 5.6)
Benzodiazepines	239	3.5 (3.1 – 4.0)
Stimulant laxatives	45	0.7 (0.5 – 0.9)
SSRIs	33	0.5 (0.3 – 0.7)
Statins	34	0.5 (0.4 – 0.7)
Cardiovascular system		
Beta-blocker in combination with verapamil or diltiazem *(risk of heart block)*	18	0.3 (0.2 – 0.4)
Amiodarone as first-line[1] antiarrhythmic therapy in supraventricular tachyarrhythmias[2] *(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)*	7	0.1 (0.05 – 0.2)
Thiazide diuretic with a history of gout[2] *(gout can be precipitated by thiazide diuretic)*	20	0.3 (0.2 – 0.5)
Phosphodiesterase type-5 inhibitors with concurrent nitrate therapy for angina[2] *(risk of cardiovascular collapse)*	2	0.03 (0.01 – 0.1)
Antiplatelet/Anticoagulant drugs		
Long-term aspirin at doses greater than 150mg per day *(increased risk of bleeding, no evidence for increased efficacy)*	24	0.4 (0.2 – 0.5)
NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination *(risk of major gastrointestinal bleeding)*	9	0.1 (0.07 – 0.3)
NSAID with concurrent antiplatelet agent(s) without PPI	117	1.7 (1.4 – 2.1)

prophylaxis *(increased risk of peptic ulcer disease)*		
Central nervous system and psychotropic drugs		
TCAs with dementia, narrow-angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention[2] *(risk of worsening these conditions)*		
Dementia	335	4.9 (4.4 – 5.5)
Narrow-angle glaucoma	13	0.2 (0.1 – 0.3)
Cardiac conduction abnormalities	3	0.04 (0.01 – 0.1)
Prostatism or prior history of urinary retention	25	0.4 (0.3 – 0.5)
Initiation of TCAs as first-line antidepressant treatment *(higher risk of adverse drug reactions with TCAs than SSRIs or SNRIs)*	75	1.1 (0.09 – 1.4)
Benzodiazepines for ≥4 weeks *(no indication for longer treatment)*	777	11.4 (10.7 – 12.2)
Antipsychotics (other than quetiapine or clozapine) in those with Parkinsonism or Lewy Body Disease[2] *(risk of severe extrapyramidal symptoms)*	51	0.8 (0.6 – 1.0)
Anticholinergics/antimuscarinics to treat extrapyramidal side-effects of neuroleptic medications *(risk of anticholinergic toxicity)*	29	0.4 (0.3 – 0.6)
Anticholinergics/antimuscarinics in patients with dementia[2] *(risk of exacerbation of cognitive impairment)*	1718	25.2 (24.2 – 26.2)
Acetylcholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil *(risk of cardiac conduction failure, syncope and injury)*	1276	18.7 (17.8 – 19.6)
Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist *(phenothiazines are sedative, have significant antimuscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccups and levopromazine as an antiemetic in palliative care)*	59	0.9 (0.7 – 1.1)
First generation antihistamines *(safer, less toxic*	635	9.3 (8.6 – 10.0)

antihistamines now widely available)		
Gastro-intestinal system		
Prochlorperazine or metoclopramide with Parkinsonism[2] *(risk of exacerbating Parkinsonian symptoms)*	13	0.2 (0.1 – 0.3)
PPI for uncomplicated peptic ulcer disease or erosive peptic ulcer oesophagitis[2] at full therapeutic dosage for >8 weeks *(dose reduction or earlier discontinuation indicated)*	1561	22.9 (21.9 – 23.9)
Oral elemental iron doses greater than 200mg daily *(no evidence of enhanced iron absorption above these doses)*	2	0.03 (0.01 – 0.1)
Respiratory system		
Theophylline as monotherapy for COPD[2] *(safer, more effective alternatives; risk of adverse effects due to narrow therapeutic index)*	65	1.0 (0.8 – 1.2)
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD[2] *(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available)*	0	0.00
Antimuscarinic bronchodilators with a history of narrow-angle glaucoma or bladder outflow obstruction[2] *(may exacerbate glaucoma or cause urinary retention)*		
Narrow-angle glaucoma	13	0.2 (0.1 – 0.3)
Bladder outflow obstruction	50	0.7 (0.6 – 1.0)
Non-selective beta-blocker with a history of asthma[2] requiring treatment *(risk of increased bronchospasm)*	30	0.4 (0.3 – 0.6)
Benzodiazepines with acute or chronic respiratory failure[2] *(risk of exacerbation of respiratory failure)*	6	0.09 (0.04 – 0.2)
Musculoskeletal system		
NSAID with severe hypertension or severe heart failure[2] *(risk of exacerbation of hypertension or heart failure)*	0	0.00
COX-2 selective NSAIDs with concurrent cardiovascular disease[2] *(increased risk of myocardial infarction and stroke)*	24	0.4 (0.2 – 0.5)
NSAID with concurrent corticosteroids without PPI prophylaxis *(increased risk of peptic ulcer disease)*	20	0.3 (0.2 – 0.5)
Urogenital system		

Antimuscarinic drugs with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism[2] *(risk of increased confusion, acute exacerbation of glaucoma and urinary retention)*		
Dementia or chronic cognitive impairment	631	9.2 (8.6 – 10.0)
Narrow-angle glaucoma	35	0.5 (0.4 – 0.7)
Chronic prostatism	122	1.8 (1.5 – 2.1)
Endocrine system		
Sulphonylureas with a long duration of action with type 2 diabetes mellitus[2] *(risk of prolonged hypoglycaemia)*	2	0.03 (0.01 – 1.1)
Thiazolidinediones in patients with heart failure[2] *(risk of exacerbation of heart failure)*	0	0.00
Analgesic drugs		
Use of oral or transdermal strong opioids as first-line therapy for mild pain *(WHO analgesic ladder not observed)*	49	0.7 (0.5 – 1.0)
Use of regular[3] (as distinct from PRN) opioids without concomitant laxative *(risk of severe constipation)*	715	10.5 (9.8 – 11.2)
Long-acting opioids without short-acting opioids for breakthrough pain *(risk of persistence of severe pain)*	610	8.9 (8.3 – 9.6)
Antimuscarinic/Anticholinergic drug burden		
Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties *(risk of increased antimuscarinic/anticholinergic activity)*	215	3.2 (2.8 – 3.6)

STOPP, Screening Tool of Older Persons Potentially Inappropriate Prescriptions; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; PPI, proton pump inhibitor; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; WHO, world health organisation; PRN, when required

[1]'First-line' therapy was determined by examining prescribing in the three months prior to starting the drug in question

[2]The use of drugs commonly indicated in certain disease conditions (such as gout, parkinsonism, glaucoma) were identified in the Enhanced prescribing Database (EPD) and used as proxies for diagnosis

[3]An opioid was defined as being used 'regularly' if a patient had received a prescription for an opioid for three consecutive months

Table 3. Logistic regression analyses investigating any PIP criteria

PIP	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Polypharmacy		
Never (ref)	1.0	1.0
Ever	7.5 (6.5 – 8.6)	7.6 (6.6 – 8.7)
Gender		
Male (ref)	1.0	1.0
Female	1.2 (1.1 – 1.4)	1.3 (1.2 – 1.4)
Age group (years)		
≤44 (ref)	1.0	1.0
45-64	0.6 (0.1 – 3.2)	0.8 (0.1 – 4.6)
65-84	0.7 (0.1 – 3.7)	0.7 (0.1 – 4.2)
≥85	0.8 (0.1 – 3.9)	0.7 (0.1 – 4.0)

Supplementary table 1. List of drugs used as proxies for conditions listed in STOPP criteria

Condition	Assumption(s) made	Drugs used as proxies listed by British National Formulary (BNF) categories [1] from which they were extracted
Supraventricular tachyarrhythmias	Presence of supraventricular tachyarrhythmias was assumed by dispensing of drug indicated for SVT	**2.1.1 Cardiac glycosides** **2.4 Beta-adrenoceptor blocking drugs** **2.6.2 Calcium-channel blockers**
Gout	Presence of gout was assumed by dispensing of drug indicated for gout	**10.1.4 Gout and cytotoxic-induced hyperuricaemia**
Angina	Criterion states 'concurrent nitrate therapy for angina'	**2.6.1 Nitrates**
Dementia	Presence of dementia was assumed by dispensing of drug indicated for dementia	**4.11 Drugs for dementia**
Glaucoma	Presence of glaucoma was assumed by dispensing of drug indicated for glaucoma	**11.6 Treatment of glaucoma**
Cardiac conduction abnormalities	Presence of cardiac conduction abnormalities was assumed by dispensing of anti-arrhythmic agent	**2.3.2 Drugs for arrhythmias**
Prostatism or prior history of urinary retention or bladder outflow obstruction	Presence of prostatism and prior history of urinary retention was assumed by dispensing of drugs indicated for BPH or for urinary retention	**6.4.2 Male sex hormones and antagonists** **7.4.1 Drugs for urinary retention**
Parkinsonism	Presence of Parkinsonism was assumed by dispensing of dopaminergic and antimuscarinic drugs used in those with Parkinson's	**4.9.1 Dopaminergic drugs used in Parkinsonism** **4.9.2 Antimuscarinic drugs used in Parkinsonism**

	disease/Parkinsonism	
Uncomplicated peptic ulcer disease or erosive peptic oesophagitis	An assumption was made that if a PPI was dispensed, it was being used for these conditions	**1.3.5 Proton Pump Inhibitors**
Moderate to severe COPD	Presence of moderate-severe COPD was assumed by dispensing of short-acting beta$_2$ agonist in combination with long-acting muscarinic antagonist, long-acting beta$_2$ agonist plus inhaled corticosteroid	**3.1.1 Adrenoceptor agonists** **3.1.2 Antimuscarinic bronchodilators** **3.1.3 Theophylline** **3.1.4 Compound bronchodilator preparations** **3.2 Corticosteroids**
Asthma	History of asthma was assumed by dispensing of beta2 agonist, inhaled corticosteroid, leukotriene receptor antagonist, theophylline	**3.1.1 Adrenoceptor agonists** **3.1.3 Theophylline** **3.2 Corticosteroids** **3.3.2 Leukotriene receptor antagonists**
Acute or chronic respiratory failure	Respiratory failure was assumed by dispensing of oxygen	**3.6 Oxygen**
Severe hypertension	Presence of severe hypertension was assumed by dispensing of ACE inhibitor (or angiotensin II receptor blocker) + calcium channel blocker + thiazide-like diuretic + alpha blocker	**2.5.5.1 Angiotensin-converting enzyme inhibitors** **2.5.5.2 Angiotensin-II receptor antagonists** **2.5.4 Alpha-adrenoceptor blocking drugs** **2.2.1 Thiazides and related diuretics** **2.6.2 Calcium-channel blockers**
Severe heart failure	Presence of severe heart failure was assumed by dispensing of ACE inhibitor (or angiotensin II receptor	**2.5.5.1 Angiotensin-converting enzyme inhibitors** **2.5.5.2 Angiotensin-II receptor antagonists**

	blocker) + beta-blocker + candesartan or spironolactone or eplerenone	**2.4 Beta-adrenoceptor blocking drugs** **2.2.4 Aldosterone antagonists**
Cardiovascular disease	Cardiovascular disease was assumed by dispensing of any cardiovascular drug, e.g. diuretics; anti-arrhythmic drugs; beta-adrenoceptor blocking drugs; drugs for hypertension and heart failure; nitrates, calcium-channel blockers, and other antianginal drugs; antiplatelet drugs; lipid-regulating drugs	**1.2 Positive inotropic drugs** **2.2 Diuretics** **2.3 Anti-arrhythmic drugs** **2.4 Beta-adrenoceptor blocking drugs** **2.5 Hypertension and heart failure** **2.6 Nitrates, calcium-channel blockers and other antianginal drugs** **2.7 Sympathomimetics** **2.8 Anticoagulants and protamine** **2.9 Antiplatelet drugs** **2.10 Stable angina, acute coronary syndromes, and fibrinolysis** **2.11 Antifibrinolytic drugs and haemostatics** **2.12 Lipid-regulating drugs**
Type 2 diabetes mellitus	Presence of type 2 diabetes was assumed by dispensing of biguanides, sulphonylureas or other antidiabetic drugs indicated for type 2 diabetes	**6.1.2.1. Sulphonylureas** **6.1.2.2 Biguanides** **6.1.2.3 Other antidiabetic drugs**
Heart failure	Presence of heart failure was assumed by dispensing of ACE inhibitor or angiotensin-II receptor antagonist in combination with a beta-blocker licensed for use in heart failure (bisoprolol, carvedilol, nebivolol)	**2.5.5.1 Angiotensin-converting enzyme inhibitors** **2.5.5.2 Angiotensin-II receptor antagonists** **2.4 Beta-adrenoceptor blocking drugs**