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Review Article

Initiatives and reforms across Scotland in recent years to improve prescribing; findings and global implications of drug prescriptions

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Abstract: Objective: Global expenditure on medicines is increasingly driven by a number of factors. These include the launch of new premium-priced medicines for complex diseases including oncology, a rise in non-communicable diseases especially with ageing populations and changes in clinical practice. There are also concerns with the rise in antimicrobial resistance due to inappropriate prescribing of antimicrobials as well as concerns with polypharmacy. Both situations increase morbidity, mortality and costs. We are aware of ongoing activities across Scotland to improve the managed entry of new medicines, including new oncology medicines, improve the prescribing of antimicrobials as well as enhance the prescribing of low-cost multiple sourced medicines and biosimilars without compromising care. In addition, we are seeking to address concerns with polypharmacy. Consequently, we wanted to document these multiple measures and their outcomes to provide an overview to inform all key stakeholders in Scotland as well as the global community as resource pressures grow. Methods: A narrative review of the literature documenting examples of ongoing national and regional initiatives across Scotland to influence future prescribing and their impact where known across multiple disease areas. Significant findings: The coordinated approach to improve the prescribing of new medicines limited the prescribing of dabigatran when first launched with recent research providing guidance on the effectiveness and safety of different direct oral anticoagulants as more are launched. The patient reported outcome measures project and other ongoing research activities, including linking datasets, is progressing under the Cancer Medicines Outcomes Programme in Scotland to improve future care with typical differences in the effectiveness of new cancer medicines in routine care versus clinical trials. The Scottish Antimicrobial Prescribing Group is also active in Scotland instigating multiple measures to improve antimicrobial prescribing. This includes improving the dosing of gentamicin and vancomycin as well as reducing the prescribing of antibiotics for women with urinary tract infections. Multiple activities have also resulted in high International Non-proprietary Name (INN) prescribing in Scotland at between 91.4% and 100% across a range of medicines. In addition, increased prescribing of low-cost multiple sourced medicines versus patented medicines in a class or related class, as well as biosimilars, leading to considerable savings without compromising care. There have also been

initiatives to address concerns with the rising costs of combination inhalers for patients with respiratory diseases as well as areas of polypharmacy with varying success. Conclusion: Multiple and coordinated approaches have improved the quality and efficiency of prescribing pharmaceuticals in Scotland. Additional measures are still needed and we will continue to monitor this situation.

Keywords: Antimicrobials, biosimilars, DOACs, generics, healthcare reforms, new medicines, oncology, polypharmacy, Scotland

Introduction

Global expenditure on medicines is rising at an annual compounded growth rate of between 3 to 6% per year [1], driven by increasing prices and expenditure on new medicines, especially those for cancer and orphan diseases, increasing prevalence of non-communicable chronic diseases (NCDs) exacerbated by ageing populations, and with it an associated increase in medicine use, as well as changes in clinical practice [2-9]. However, there are concerns that new medicines for orphan diseases and cancer are being funded at high prices, despite often limited clinical data available at launch and often limited health gain, due to the emotive nature of these disease areas [2, 3, 6, 10-13]. High prices for new medicines are a concern to a number of European countries, especially Central and Eastern European (CEE) countries, impacting access and funding [14-18].

There are also concerns with rising rates of antimicrobial resistance (AMR) across countries due to inappropriate prescribing and dispensing of antimicrobials, increasing morbidity, mortality and costs [19-22]. The situation has been exacerbated with the recent COVID-19 pandemic with often high rates of inappropriate antimicrobial prescribing [19, 23-25]. There are also growing concerns with inappropriate polypharmacy, increasing adverse reactions, morbidity, mortality and costs [26-33]. Appropriate polypharmacy has been defined in Scotland as '(a) all drugs are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with by the patient; (b) therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future; (c) drug therapy has been optimised to minimise the risk of adverse drug reactions (ADRs) and, (d) the patient is motivated and able to take all medicines as intended' [28].

Consequently, there is an urgent need to ensure that available resources are used as appropriately as possible, given the need to balance available resources against unmet need [2, 34]. As a result, we address key issues including opportunity costs [35-37].

Scotland has introduced multiple initiatives and measures in recent years to improve the quality and efficiency of prescribing across sectors for both new and established medicines, with these activities typically inter-related. Activities include a structured approach to the introduction of new medicines orchestrated by the Scottish Medicines Consortium (SMC) as well as measures to increase the prescribing of multiple-sourced medicines (generics) versus originators and patented medicines in a class or related class and biosimilars [38-42]. There have also been multiple initiatives in Scotland concerning the management of respiratory conditions, given the increasing use and costs of combination inhalers, alongside addressing concerns with polypharmacy [28, 43-45].

There is a need to consolidate these initiatives and their outcomes to inform key stakeholders in Scotland as well as the global community as resource pressures grow. This is particularly important for low- and middle-income countries (LMICs) struggling to attain or retain universal healthcare in the face of growing pressures. Our findings will build on our earlier paper describing ongoing initiatives to enhance the prescribing of multiple sourced medicines in Scotland and their impact [46]. This is particularly important in Scotland with expenditure on medicines expected to rise to 32.5% of total ambulatory care expenditure by 2028/2029, up from 28.3% in 2018/2019, and in hospitals from 7.2% of total hospital expenditure in 2018/2019 to 12.4% in 2028/2029 [43]. Consequently, savings will need to be made elsewhere with this envisaged growth in medicines' expenditure outstripping growth generally healthcare spending in Scotland [43]. This situation needs to be avoided if possible.

We are aware that there have been a number of published reviews analysing the effectiveness

of different interventions to reduce inappropriate prescribing of medicines [47-50]. However, we are unaware of studies that have documented ongoing and inter-related activities across multiple situations within a country to improve prescribing. This was the aim of this paper.

Materials and methods

We principally undertook a narrative review of the literature. This includes examples in Scotland where limited demand-side activities have been instigated, their rationale and subsequent impact. This builds on our earlier published paper documenting multiple measures that had been introduced to increase the prescribing of multiple sourced medicines without compromising care [46].

The chosen examples, and their contextualisation, are based on the considerable knowledge and experience of the co-authors. We adopted this approach rather than an extensive review of peer-reviewed publications since our objective was principally to document multiple examples across Scotland, and subsequently contextualise these, to provide future direction rather than undertake a formal systematic review. This is because there have already been a number of systematic reviews examining the effectiveness of different interventions to reduce inappropriate medicine use [47-51]. We have used this approach before when debating key issues surrounding the introduction of new medicines, biosimilars, multiple-sourced medicines and fixed-dose combinations [2, 3, 19, 41, 52-58].

We have concentrated on medicines given their growing use and expenditure across countries including Scotland, especially with ageing populations [1, 2, 43].

Demand-side measures will be captured using the 4E approach: Education, Engineering, Economics and Enforcement [59, 60]. Education includes encouraging International Non-proprietary Name (INN) prescribing through educational initiatives, developing and communicating guidelines and formularies and undertaking audits of prescribing practices [46, 61-63]. Education also includes auditing compliance with guidelines in routine clinical care [64]. Engineering includes managerial or organizational interventions including monitoring prescribing against quality targets [40, 41, 59, 60, 65]. Economics includes financial incentives including payment to physicians for attaining agreed prescribing targets [46, 61]. Enforcement includes regulations by law [59, 60]. Examples of enforcement include compulsory generic substitution and laws banning the dispensing of antibiotics in pharmacies without a prescription [56, 58, 66, 67]. However, this type of enforcement is not present in Scotland with for instance community pharmacists unable to substitute an originator with a multiple sourced (generic) medicine without authorisation from the prescriber [40, 41, 46].

Results

We will first document key organisations involved across Scotland with improving the quality and efficiency of prescribing. Subsequently, review ongoing initiatives surrounding new medicines, those enhancing the appropriate use of antimicrobials across sectors as well as enhancing the utilisation of multiple-sourced medicines and biosimilars without compromising care. Finally, we will discuss multiple ongoing initiatives to address issues and concerns with the prescribing of combination and other inhalers for patients with asthma and chronic obstructive pulmonary disease (COPD), as well as concerns with inappropriate polypharmacy.

Key organisations in NHS Scotland

Table 1 summarises a number of ongoing and inter-related activities both nationally and regionally across Scotland. These include linking advice from key national groups including SMC, the Scottish Intercollegiate Guidelines Network (SIGN), the Scottish Antimicrobial Prescribing Group (SAPG), as well as Scottish Government groups to instigate multipronged but consistent messaging. The Scottish Health Boards (Regions) typically build on these initiatives. In both situations, quality indicators have been developed to improve future prescribing [40, 68-70].

Newer medicines

The advice to prescribe dabigatran, in line with guidance from Healthcare Improvement Scotland (**Table 1**), resulted in limited use initially; however, its use increased following prescribing advice from SMC [106]. There was also greater prescribing of dabigatran, as the first direct oral anticoagulant (DOAC), among rural populations without the need for constant monitoring as seen with warfarin [106].

Table 1. Key organisations in NHS Scotland involved with improving the quality and efficiency of prescribing of medicines

Organisation	Goals and summary of activities
National	
Scottish Medicines Consortium (SMC) [42, 43, 71, 72]	● SMC considers a broad range of evidence when deciding which medicines should be accepted for use and funding within NHS Scotland. This includes possible prescribing restrictions as well as potential prices for new medicines, including any negotiated price reductions through patient access schemes (managed entry agreements-MEAs), following an assessment of their value based on quality adjusted life years (QALYs). Multiple stakeholders are typically included in the decision making. ● One principal group within SMC includes the New Drugs Committee (NDC), which consists of physicians, pharmacists and pharmaceutical company representatives. The remit of the NDC is to summarise key clinical and economic considerations for new medicines prior to review within SMC meetings, with the NDC offering preliminary advice to companies before SMC reviews final submissions to enhance their content. ● Evidence from patient groups and where appropriate, the Patient and Clinician Engagement process, is also considered by SMC when reviewing the role and value of new medicines. ● A key part of SMC's activities since 2003 is to improve financial planning for new medicines with a likely appreciable budget impact in Scotland (> £500,000 per annum by the time their use reaches a steady state) through providing advanced intelligence is via its Horizon Scanning activities. Each October SMC produces a Forward Look report including information on potential new medicines together with an accompanying financial spreadsheet. The report incorporates clinical data including indications, likely comparators and predicted financial impact including the potential for any MEAs, which involves a range of key stakeholders including pharmaceutical companies. Pharmaceutical companies are important to help verify the content including likely timelines for any launch as well as potential budget impact.
Scottish Intercollegiate Guidelines Network (SIGN) [73]	● The goal of SIGN is to improve the quality of clinical care and prescribing in Scotland by reducing variation in practice and outcomes achieved through the development and dissemination of robust national clinical guidelines containing recommendations for improving care. ● These include guidelines advocating higher dose statins for patients with coronary vascular disease and diabetes following evidence such as the Heart Protection Study [40, 74-76]. ● Adherence to guidelines is increasingly recognised as an important indicator for assessing the quality of prescribing across sectors versus the World Health Organisation/International Network for Rational Use of Drugs (WHO/INRUD) criteria in ambulatory care, which includes prescriptive measures such as the number of medicines per physician encounter and the number of encounters where an injection is prescribed [41, 62, 77-80]. ● There have been useful collaborations among the National agencies in Scotland to enhance consistency of messaging and avoid duplication of effort. Examples include: ○ In 2020 SIGN published a guideline addressing the management of suspected lower Urinary Tract Infection in adult women (SIGN 160) [81]. SAPG proposed the guideline and contributed significantly to its development. ○ Whilst SIGN does not assess the cost-effectiveness of medicines including new medicines (remit of SMC), if SMC has given an opinion on the potential role and value of a new medicines this advice is contained within the appropriate guideline. It is believed this consistency of messaging from initial assessment by SMC through to national clinical guidelines enables clarity for prescribers and those advising them including relevant personnel within the Health Boards.
Scottish Antimicrobial Prescribing Group (SAPG), Scottish Infection Research Network (SIRN); Scottish Surveillance of Healthcare Infection Programme (SSHAIP)	● SAPG was established in Scotland in 2008 to promote the safe and effective use of antibiotics across all sectors hosted by Healthcare Improvement Scotland, and delivered by Health Board Antimicrobial Management Teams (AMTs) [82-85]. SAPG aims to identify and promote ways to optimise the use of antimicrobials to prevent and treat infections, minimise antimicrobial resistance and reduce harm to both patients and wider society [82]. ● Activities incorporate a national framework for antimicrobial stewardship (AMS) and include: ○ National and local surveillance of antimicrobial use and resistance supplemented by regular point prevalence surveys in hospitals using agreed formats to improve future use by identifying areas of concern [82, 83, 85, 86]. ○ Audits of clinician prescribing against regularly updated empirical prescribing guidance and national indicators including prescribing for surgical prophylaxis as per SIGN recommendations [87]. ○ Promotion of antimicrobial stewardship ward rounds and regular prescriber education coordinated by AMT members [84]. ○ Development of evidence-based processes to support safe and effective penicillin allergy de-labelling within hospitals to reduce risks associated with prescribing of non-penicillin based antibiotics [88]. ● SIRN was formed in 2006 to build a sustainable high quality research infrastructure regarding hospital associated infections (HAIs). Recent studies include Pan *et al.* (2019) who showed that antimicrobial exposure in the community was an independent risk factor for hospital acquired *Clostridioides difficile* infections; consequently, this should be considered as part of any risk assessment of patients who develop diarrhoea whilst in hospital [89]. ● SSHAIP also works closely with these groups. Ongoing programmes including monitoring trends with surgical site infections with subsequent activities to reduce prolonged antibiotic use, which can be a problem across countries [90, 91].

Cancer Medicines Outcomes Programme (CMOP)	● The CMOP programme in Scotland was developed to test the connectivity and linkage of evolving national and local datasets to help determine the clinical outcomes of different cancer medicines given often the paucity of clinical data at launch, patients in clinical practice often having more co-morbidities than those enrolled into clinical trials and the ever increasing costs of new cancer medicines [3, 92-94]. ● A secondary objective is to test the feasibility of routinely collecting and analysing of patient reported outcome measures (PROMs) including quality of life data during routine clinical practice to inform future management [95]. ● Using real-world data should help key stakeholder groups in Scotland assess the true value of new cancer medicines using health technology assessment methodologies as often initial submissions for new cancer medicines to SMC use modelling based on clinical studies pre-launch with only a limited number of selected patients and surrogate endpoints [3, 93, 95]. ● Current cancers of interest include head and neck, cervical, endometrial, vulval, prostate and colorectal carcinomas as well as multiple melanoma and myelomas [92].
Prescribing guidance including quality indicators	● In addition to national activities by SIGN, other initiatives to improve the quality of prescribing include: ○ Agreed National Therapeutic Indicators and their visualisation including indicators for infection (total, those for UTIs in conjunction with initiatives with SAPG and a reduction in CDIs through monitoring prescribing of target antibiotics including cephalosporins, clindamycin, co-amoxiclav and fluoroquinolones), polypharmacy and anticholinergics in the elderly [96-98]. ○ Prescribing guidance from Healthcare Improvement Scotland as well as Health Boards for dabigatran was first launched for the management of atrial fibrillation balancing the risks and benefits given concerns with potentially excessive bleeding in the elderly [99], with this approach endorsed by subsequent revelations that the company withheld important information [100]. ● Physicians in Scotland trained (starting in medical school) to prescribe by international non-proprietary name (INN) and followed-up in ambulatory care with the help of decision-support software and by Health Boards with prescribing by INN seen as good-quality prescribing [40, 46, 61, 101]. There are a number of exceptions (Box 1A) where brand name prescribing is encouraged based on safety concerns; however, these are limited. Such activities are aided in the UK by the fact that community pharmacists are not allowed to substitute an originator for a generic when a physician prescribes a branded (originator) medicine without prior authorisation [40, 102]. ● Multiple initiatives nationally and regionally to enhance the prescribing of multiple sourced medicines within a class or related class to conserve resources without compromising care including educational initiatives, quality targets and financial incentives [38-40]. ● There have also been educational and other activities including national prescribing targets for both new and switched patients across Scotland in recent years to enhance the prescribing of lower cost biosimilars where appropriate to save costs without compromising care [41, 57, 103, 104]. These activities have accelerated since the publication of the NOR-SWITCH study on biosimilar infliximab sponsored by the Norwegian Government which showed no difference in effectiveness and safety between the biosimilar and originator [41, 105].

The prescribing of the DOACs have grown across Scotland as physicians gained more experience, which has resulted in two of the DOACs now among the top ten medicines by expenditure in Scotland [43]. Indirect comparisons have now taken place to provide prescribing advice to healthcare professionals in Scotland in the absence of comparative Phase III trials [107]. Mueller *et al.* (2019) found that whilst there were no observed differences between the different DOACs with respect to the risk of systemic embolism, stroke or cardiovascular death, the risk of a myocardial infarction was greater among patients prescribed apixaban [107]. The risk of pulmonary embolism, gastrointestinal bleeds, major bleeds and all-cause mortality was also greater among those prescribed rivaroxaban [107]. Encouragingly, adherence to DOACs was found to be reasonably high [108]. A follow-on study, which included patients from other Western European countries, showed that persistence and adherence among the various DOACs were similar [109]. However, first year persistence and adherence rates were lower with dabigatran [109], and remained lower throughout the follow-up period, providing guidance to physicians along with assessing different safety and effectiveness parameters [107, 109].

Early studies from the Cancer Medicines Outcomes Programme (CMOP) (**Table 1**) have now been published. These included evaluating the costs of using either abiraterone or enzalutamide to treat resistant prostate cancer patients [110], and treatment outcomes among the metastatic prostate cancer population [94]. Of interest is that Baillie *et al.* (2020) showed overall survival was typically poorer in routine clinical care versus the pivotal trials [94], which is important when assessing their subsequent role and value. Identified factors influencing survival in these patients included their baseline performance status, alkaline phosphatase, albumin and prostate-specific antigen [94].

The patient reported outcome measures (PROM) project and other ongoing research activities, including linking datasets, is progressing under CMOP among patients with different cancers to provide future guidance [95]. This is important given concerns when only limited clinical data is submitted to SMC to support funding at premium prices (**Table 1**), and following the findings of Baillie *et al.* [94].

Data sets are also being linked to assess differences in adherence and persistence among other biological medicines to manage patients with a range of rheumatic musculoskeletal diseases, including rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, in their home environment. Approximately half of the patients were persistent on their initial biologic treatment, and among those who discontinued treatment, the majority were re-initiated with the same biologic medicine [111]. Adherence rates during treatment was over 80% for the three conditions, with no obvious difference between the different biological medicines used [111]. Consequently, other factors such as costs, convenience, and patient preference should be borne in mind when healthcare professionals select biologicals to manage patients with rheumatic diseases.

Infectious diseases

Multiple activities have taken place under SAPG and other organisations (**Table 1**) to improve antibiotic prescribing in Scotland.

AMS programmes among hospitals in Scotland have reduced the prescribing of high-risk antimicrobials thereby reducing *Clostridioides difficile* infection (CDI) rates [112]. However, barriers still exist, which need addressing going forward [113].

The multifaceted quality improvement programmes instigated by SAPG have resulted in a reduction in the prescribing of carbapenems and piperacillin/tazobactam [83]. However, there were concerns that review/stop dates for both antibiotics were poorly documented, which is currently being addressed [83]. Alongside this, in 2009, SAPG introduced national resources to improve the administration of gentamicin and vancomycin given concerns. A multifaceted programme, including guidelines and educational material, online and mobile app dose calculators, resulted in the recommended gentamicin dose being administered increasing from 44% to 89% of administrations between 2011 and 2018 [114]. For vancomycin, the correct loading dose increased from 50% to 85% of occasions and the correct maintenance dose from 55% to 90% [114].

There have also been multiple and co-ordinated activities to reduce prescribing of antibiotics for women with urinary tract infections (UTIs)

(**Table 1**) [115]. These initiatives resulted in a lower number of urine specimens being produced and sent for culture, an increase in promoting self-care measures especially for women with mild UTIs or a limited number of symptoms, delayed antibiotic prescribing as well optimal use of empirical antibiotic prescribing when clinically appropriate [115].

SAPG has also been involved with the development of a software application giving practitioners easy and quick access to clinical guidance, including dosage calculators for key antibiotics, a decision aid to support the management of UTIs in older people as well as an audit tool [116].

However, we are aware that there can be unintended consequences of policy changes. Hospitals across Scotland changed from cephalosporins to combinations including gentamicin to prevent surgical site infections (SSIs) as part of ongoing initiatives to reduce CDIs. However, rates of acute kidney injury (AKI) increased in orthopaedic patients who were given flucloxacillin plus gentamicin [117]. Consequently, these patients should be regularly monitored along with suggestions that gentamicin should be avoided in orthopaedic patients undergoing surgery in the perioperative period. Following these findings, there was a change from recommending flucloxacillin and gentamicin to co-amoxiclav [118]. This resulted in a reduction in the rate of post-operative AKIs without any increase in CDIs [118]. Consequently, this policy is being continued. The antibiotic policy change was not associated with a significant increase in AKI in the other patient groups.

More recently, antibiotic prescribing for hospital patients with respiratory tract infections (RTIs) with suspected or proven COVID-19 has been observed despite concerns of a predominantly viral nature [19, 119, 120]. Antifungal prescribing was also observed in critical care units in hospitals in Scotland in patients with RTIs with suspected or proven COVID-19 [121]. Both situations indicate the importance of AMS activities given the relatively low number of COVID-19 patients in reality with concomitant bacterial or fungal infections [19, 24, 120]. The rationale for increased prescribing is currently being investigated as a prelude to undertaking future measures given concerns with AMR [19, 23].

Interestingly, a recent study has shown a reduction in the prescribing of antibiotics in ambulatory care in Scotland following a steep rise during the early stages of the COVID-19 pandemic [122]. This initial increase is thought to be due to an increase in the prescribing of treatments for exacerbations of COPD, with patients with COPD considered at high risk for COVID-19 and its impact [123-125]. This resulted in most GPs providing treatments for these patients to be on hand in their homes at the start of the pandemic should the need arise. Potential reasons for reduced prescribing in the months following the initial outbreak include patients being more likely to practice self-care, improved hand hygiene and following of educational and other initiatives to reduce the spread of the virus to protect the NHS during this time [122].

Initiatives to increase the prescribing of multiple sourced medicines in a class or related class

Encouraging INN prescribing in Scotland: As documented in **Table 1**, physicians in Scotland are trained to prescribe by INN rather than by brand name, enhanced by multiple studies showing no difference in outcomes between approved generics from regulatory bodies such as the European Medicines Agency and the Food and Drug Administration and originators [126-130]. As a result, there is typically high INN prescribing in Scotland with trust in the effectiveness and safety of generics, which range from 91.4% to 100% across a number of medicines and classes (Table S1) where there are no concerns (Box 1A). The situation can be different among LMICs where there can be concerns with the quality of generics challenging routine INN prescribing [131-134]. Initiatives such as the Lomé initiative in Africa to address sub-standard medicines is a key step forward building on earlier initiatives [41, 135-137].

There were issues with the effectiveness and safety of generic clopidogrel when first launched, exacerbated by activities from the originator company [138]. Concerns with a different salt for the initial generics were unfounded, resulting in the originator company eventually being fined by the French Government for their misinformation [138-140]. More recently, the company manufacturing LYRICA threatened court action if GPs in Scotland prescribed pregabalin, i.e., by INN rather than LYRICA, for

patients with neuropathic pain as this indication was still patented [141]. This resulted in Community Pharmacy Scotland issuing advice indicating that physicians should stay within the current licence when the indication is known [141, 142]. Encouragingly, there was no similar situation when the first indication for a number of oral cancer medicines recently lost their patents given ever rising expenditure for oncology medicines in Scotland [3, 143].

INN prescribing can also address issues of confusion if patients are dispensed different named branded generics on each occasion [41, 66, 144]. Such activities could lead to over and under-dosing unless the prescribing physicians, and/or dispensing pharmacist, spends time with patients re-assuring them that the medicines they are being prescribed or dispensed are the same [144-146]. This is addressed in the UK with packs of multiple sourced medicines just including the INN name, tablet strength and the name of the manufacturer [41], with the prescription not changing.

The 'M' (Manufacturer) and 'W' (Wholesaler) scheme was introduced in the UK in April 2005 to increase transparency in the pricing of generics including current discounts and rebates in the system [41, 61, 147]. These measures resulted in appreciable price reductions typically ranging from 88% to 95% versus pre-patented originator prices (Table S2), which resulted in considerable savings. High INN prescribing rates means these savings are realised from the first day multiple sourced medicines are listed at a reduced price in the drug tariff in Scotland.

Encouraging the preferential prescribing of multiple sourced medicines within a class or related class: There have been numerous initiatives in Scotland (**Table 1**) to enhance the prescribing of multiple sourced medicines within a class or related class given the considerable price reductions seen in practice (Table S2) coupled with high levels of INN prescribing (Table S1).

Key classes include lipid lowering therapies including statins, medicines affecting the renin-angiotensin system and selective serotonin reuptake inhibitors (SSRIs). In the case of statins, there were limited perceived differences between them (**Table 2**) [61]. More recently higher dose statins, e.g., up to 80 mg atorvastatin, are recommended by SIGN (**Table 1**) in patients with established coronary vascular disease [74]. High dose atorvastatin was advocated due to safety concerns with high dose simvastatin and limited differences in price once generic atorvastatin became available (Table S2) [148]. There were though concerns of potentially increased side-effects with higher dose statins, interfering with adherence [75]. However, this did not turn out to be the case with adherence rates considerably higher among patients prescribed higher dose statins. This may be because these patients will have a higher risk of serious cardiovascular events if not taking their prescribed statins, and, as a result, be more receptive to advice encouraging adherence [75]. Other national and regional activities included limiting the prescribing of ezetimibe (**Table 2**) [40].

There were concerns with the extent of Angiotensin Converting Enzyme Inhibitor (ACEI) induced cough and bronchospasm potentially impacting on adherence in practice [101]. However, prospective studies showed an ACEI-cough only occurred in approximately 10% of patients, and only 2% to 3% of patients discontinued ACEIs due to an ACEI-cough in the clinical trials [101], although rates can be higher in selected populations [101, 149]. Consequently, where possible, ambulatory care physicians in Scotland were encouraged to prescribe multiple sourced ACEIs first line versus angiotensin receptor blockers (ARBs) (**Table 2**). However, no specific activities were undertaken when the first generic ARB (losartan) became available (**Table 2**).

There are concerns whether health authorities should be prescriptive with advocating specific treatments within a class or related class among patients with mental health disorders [150]. However, Sweden introduced measures to limit the prescribing of duloxetine due to concerns with its effectiveness and safety versus other second-line antidepressants [151]. Scotland also introduced a variety of initiatives to influence the prescribing of different SSRIs to good effect (**Table 2**) [38]. This included switching patients from patented escitalopram to considerably less expensive multiple-sourced citalopram without compromising care, which mirror tactics in other disease areas to address

Table 2. Multiple initiatives to enhance the prescribing of lower costs medicines in a class or related class and their outcomes

Medicine Class	Instigated Measures	Outcome
ACEIs and ARBs		
ACEIs vs. ARBs [46, 101]	● Education-National and Regional prescribing guidance including SIGN, benchmarking among physicians in the same Health Board and academic detailing. ● Economics-Financial incentives for achieving prescribing goals including prescribing targets. ● Engineering-Prescribing targets for ACEIs and ARBs as a % of all renin-angiotensin prescriptions. These include <25% for ARBs by prescribing volume (Lothian Health Board).	● Total utilisation of ACEIs was 81.2% of both ACEIs and ARBs in 2007 (DDD based), similar to Austria and Croatia which had introduced prescribing restrictions for ARBs (Enforcement). ● Utilisation of ACEIs in Scotland was considerably higher than Portugal at 55% of ACEIs and ARBs at the end of 2007 with limited demand side reforms introduced in Portugal. ● Overall expenditure on ACEIs and ARBs remained stable in Scotland between 2001 and 2007 despite a 159% increase in utilisation helped by high use and low prices for generic ACEIs (**Tables 1** and **2**). This compares with total expenditure on ACEIs and ARBs in Portugal 2.4 times higher in 2007 versus Scotland when adjusted for population size.
ARBs [46, 154, 155]	● No specific demand side reforms were instigated in Scotland when generic losartan became available as the first generic ARB, with a Cochrane review concluding all ARBs have a statistically equivalent effect on blood pressure. ● This was deliberate policy as: ○ Multiple demand-side measures had already been successful in limiting ARB utilisation in Scotland in the first place. ○ Generic valsartan and candesartan would soon become available adding to the savings from generic losartan. ○ Other higher priority areas had already been identified to improve the quality and efficiency of primary care prescribing in Scotland at the time generic losartan became available. ○ Potentially confusing messages moving from prescribing ACEIs first line to ACEIs and generic ARBs first line.	● No significant change in the utilisation pattern of losartan or the other single ARBs combined before or after the introduction of generic losartan. ● Losartan accounted for 32% of total ARBs 12 months after listing leading to estimated savings of nearly GB £8 million per year from the availability of generic losartan alone vs. the pre-patent loss situation.
Lipid lowering therapies [40, 61]	● Education-National and Regional guidelines advocating generic statins first line, e.g., simvastatin, academic detailing and general monitoring of physician prescribing habits, benchmarking physicians; educational initiatives including SIGN guidance advocating high dose statins and that ezetimibe should only be prescribed by specialists when cholesterol targets are not reached on maximal tolerated statins. ● Economics-Practice based financial incentive schemes to encourage the preferential prescribing of generic statins; Payment by result schemes surrounding the statins; incentive schemes to reduce the prescribing of ezetimibe. ● Engineering-Better Care Better Value' indicators to enhance the prescribing of low cost statins; quality targets for low cost statins as well as proportion of ezetimibe compared to total ezetimibe and statins; therapeutic switching by Health Board pharmacists when working with GPs including patented to multiple sourced statins and deprescribing of ezetimibe without compromising care.	● Appreciably increased prescribing of lower cost multiple sourced (generic) statins (**Tables 1** and **2**) coupled with reduced prescribing of ezetimibe (72% reduction between 2010 and 2015) and increasing prevalence rates of cardiovascular disease in Scotland resulted in a 50% reduction in reimbursed expenditure on lipid-lowering therapies in Scotland between 2001 and 2015 despite a 412% increase in their utilization. ● Utilisation of higher doses of atorvastatin (40 mg and 80 mg) and simvastatin (40 and 80 mg) accounted for 71.3% of total usage of these statins (items dispensed) in 2015 up from 17.3% in 2001.
SSRIs [38, 46]	● Education-Fluoxetine and citalopram initially recommend with sertraline added especially once multiple sources became available; reviews of antidepressant prescribing especially if patients on long-term antidepressants; subsequently concerns with escitalopram and citalopram and QT prolongation leading to recommendations for fluoxetine and sertraline (sertraline recommended in patients with cardiovascular disease). ● Economics-Practice incentive schemes especially surrounding escitalopram. ● Engineering-Prescribing targets for escitalopram; active switching programmes in some Health Boards from escitalopram to citalopram with frequent monitoring of patients (until QT concerns); subsequent reviews on patients prescribes citalopram and escitalopram following concerns with QT prolongation.	● These multiple measures combined with high INN prescribing rates and low costs for generics once available (**Tables 1** and **2**) resulted in a 73.7% reduction in SSRI expenditure between 2001 and 2017 despite a 2.34-fold increase in their utilisation. ● Increased utilisation of SSRIs has been assisted by increasing number of patients accessing mental health services, recommended for first line treatment especially after generic availability; increasing long-term use with regular reviews and widening the indications for SSRIs. ● Overall, there has been low utilisation of escitalopram in Scotland in recent years reaching a maximum of 6.99% of total items dispensed in 2007 before falling to 2.1% of total items dispensed in 2017 following concerns with QT prolongation. ● There was a significant decrease in the combined prescribing of citalopram and escitalopram following concerns with QT prolongation along with a corresponding significant increase in the prescribing of sertraline, which is continuing.

NB: ACEIs, angiotensin converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; SSRIs, selective serotonin re-uptake inhibitors.

the 'ever greening' activities of pharmaceutical companies [38, 152, 153].

Similar initiatives have been undertaken to enhance the prescribing of multiple sourced proton pump inhibitor (PPIs) when available with limited perceived differences between them (Table S3) [39, 46, 61]. This is important with omeprazole currently the most prescribed medicine in Scotland [43]. There were also initiatives to encourage the prescribing of the lowest possible dose, and review patients on long term PPIs at least annually, to reduce potential side-effects from long-term use [39, 156]. This built on earlier advice from NHS Scotland to encourage the prescribing of maintenance rather than healing doses of PPIs [157].

The situation with inhalers, especially combination inhalers, to treat patients with asthma and COPD is different (**Table 2**). There is increasing recognition of the need to treat these patients well especially with COPD, the only major cause of death to increase in Scotland in recent years [44]. New higher priced patented devices have been developed to address concerns with their use, with poor inhaler technique and adherence known to considerably increase morbidity and costs. However, the considerable expenditure on combination inhalers in recent years has enhanced National and Health Board focus on them [43, 44, 158]. As a result, there has been an increased focus and prescribing of lower cost Fostair® (beclomethasone/formoterol) and Revlar® (fluticasone furoate/vilanterol) following recommendations by Health Boards as more formulations are being launched with different steroid doses [44, 159]. The availability of different steroid doses is important with ongoing moves to reduce the steroid burden among patients in view of potential consequences [44]. There have also been multiple activities by the Health Boards to reduce over-reliance on short-acting beta-agonists (SABAs) as this often indicates poor asthma control and is a predictor for future risk of asthma attacks [160]. In Lothian, these activities resulted in the percentage of patients prescribed more than 12 SABAs per year falling from 10.6% of those prescribed SABAs in 2016 to 8.8% in 2021. However, there is still room for improvement [160].

We are aware though there are classes of medicines where it can be difficult to be prescriptive about the prescribing of multiple sourced medicines first line versus patented medicines in a class [150]. This includes the atypical anti-psychotics where the choice of first line treatment for patients with bipolar disease and schizophrenia will typically vary depending on the patient and their characteristics [161-164]. As a result, there were no specific demand-side initiatives preferentially encouraging the prescribing of risperidone when generics first became available in Scotland, with savings accumulating as more atypical antipsychotics become available as generics [161]. This includes quetiapine as expenditure on quetiapine was the fifth highest of any medicine in Scotland in 2020 [43]. This is different though to initiatives discouraging the prescribing of antipsychotics in elderly patients with dementia in view of increased morbidity and mortality [165, 166].

Biosimilars: Biosimilars are increasingly welcomed given ever rising expenditure on biological medicines for complex diseases including immune diseases, oncology and orphan diseases [1, 41].

Table 3 builds on **Table 1** and captures a number of activities across Scotland to promote biosimilars and their impact.

We are aware there are circumstances when it can be problematic to switch patients between an originator and biosimilar without additional patient education as seen with biosimilar insulin glargine. New patients may be started on a named biosimilar, especially with prices falling as more biosimilars are launched [168, 169]. However, there are concerns with switching between an originator and a biosimilar insulin glargine as there are different devices, which may impact on adherence rates without patient education [168-170]. As a result, in 2020 there was low utilisation of biosimilar insulin glargine in Scotland at only 19.5% of total insulin glargine (DDD basis) [170]. This was not helped by currently limited price differences between the originator and biosimilar (7.5%), which is unlike the situation seen with adalimumab in the United Kingdom [170, 171].

Polypharmacy

There are a number of ongoing programmes to reduce inappropriate polypharmacy across Scotland (Box 1B and Table S4). A quality

Table 3. Multiple activities in Scotland to enhance the prescribing of biosimilars when first available and their impact

Biosimilars and references	Summary of ongoing activities	Outcome
Biosimilars for etanercept, infliximab, trastuzumab and adalimumab [41, 65, 69, 103, 104, 167]	• Education-Multiple educational initiatives among all key stakeholder groups including a national prescribing framework launched in 2015 and updated in 2018; publication of studies outlining experiences and lessons learned with biosimilars by NHS Boards including switching patients from originators to biosimilars. • Engineering-Prescribing targets for biosimilar use including % of new patients started on a biosimilar vs. an originators as well as % switch patients; Health Boards (Regions) regularly benchmarked against each other with findings broadcasted. • Economics-Continual pressure by Health Boards to encourage the prescribing of lower costs biosimilars where possible with ongoing pressure on budgets; some of the resources released used to treat more patients with biological medicines as well as fund additional clinical personnel to improve patient care.	• By December 2017, etanercept and infliximab biosimilars had reached 84% and 94% respectively of the total utilisation of these biologicals. • By December 2017; biosimilar rituximab had reached 74% of total rituximab - the first year of its availability. • By December 2019, biosimilars for trastuzumab had accounted for 92% of all trastuzumab. • By December 2019, biosimilar adalimumab had reached 87% of total adalimumab and growing.

improvement project in NHS Forth Valley showed that there were substantial and sustained reductions in the high-risk prescribing of NSAIDs in older people as well as NSAIDs prescribed alongside oral anticoagulants [172]. However, there was no effect on the prescribing of antipsychotics among older people in Scotland, exacerbated by different stakeholders involved including geriatricians and psychogeriatrician, with GPs reluctant to change prescriptions despite concerns [166, 172].

Recent data from NHS Scotland also showed a decline in the elderly co-prescribed medicines likely to increase AKI as well as sulfonyl ureas as a result of multiple activities **Table 1**) [96, 173]. The percentage of elderly patients (65 years or older) co-prescribed an NSAID, ACEI/ARB and a diuretic as a percentage of elderly patients prescribed an ACEI/ARB and a diuretic decreased from 0.74% across Scotland in October to December 2015 to 0.39% in April to June 2021 [96]. The number of patients aged ≥75 years prescribed sulfonylureas as a percentage of the elderly prescribed anti-diabetic medicines across Scotland also decreased from 44.81% in October-December to 32.76% in April to June 2021 [96].

However, there are still areas of concern including the prescribing of anticholinergic and antipsychotic medicines in the elderly with limited changes in the past five years [96]. The percentage of the elderly, ≥75 years, dispensed >10 items of strong or very strong anticholinergics per annum as a percentage of all elderly was 7.24% in October to December 2015 and 7.11% in April to June 2021 [96]. This is a concern as such medicines are linked with increasing falls and fractures as well as delirium. Similalry, the percentage of elderly prescribed an antipsychotic across Scotland remained relatively steady at 2.56% in October to December 2015 and 2.91% in April to June 2021 [96].

Discussion

We believe this is the first paper to consolidate the range of national and regional activities across Scotland in recent years, including multipronged and consistent messaging, to improve the quality and efficiency of prescribing. These typically include multiple activities, building on similar findings in other countries and other situations [41, 47, 51, 60].

The multifaceted approach to improve the managed entry of new medicines in Scotland including post-launch assessments, building on the examples with oncology medicines under the CMOP programme (**Table 1**) and the DOACs, is welcomed. This is especially welcomed with new oncology medicines often launched at high

prices, concerns with their access and value especially in LMICs, sparsity of comparative clinical data at launch, and the use of surrogate markers in the early trials [2, 3, 12, 16, 17, 93]. The growth in expenditure for medicines dispensed in hospital, including new biological medicines, is predicted to drive increased expenditure on medicines in Scotland in the coming years [43]. Consequently, their value needs to be increasingly scrutinised as increased costs will necessitate reductions in expenditure in other components of care if budgets are not increased [43]. Future suggestions include expanding the remit of SMC to re-look at MEAs of patented oncology and other medicines if the medicines used in submissions subsequently become available as either low-cost oral generics or biosimilars [3].

The value of this comprehensive approach was seen following the launch of dabigatran where excessive bleeding was avoided in countries and regions that had instigated educational and other activities pre-launch [106]. Sweden also provides an exemplar for a co-ordinated approach to the managed entry of new medicines. This again starts with extensive horizon scanning and budgeting activities, and ends with post-launch assessments [174-178]. Examples include new second-generation direct-acting antivirals (DAAs) for hepatitis C, which is also welcomed in Scotland as these medicines constituted the highest expenditure category in 2019 [43, 178]. Such activities will grow across countries given ever likely higher prices for new medicines in complex disease areas including cancer and orphan diseases [3, 41].

The comprehensive programmes to improve the utilisation of antimicrobials in Scotland (**Table 1** and Section 3.3) have again shown that multiple initiatives are needed to influence prescribing. This mirrors the experiences seen in former Soviet Union Republics where multiple initiatives have reduced prescribing and dispensing of antibiotics as well as limited any increase in their utilisation where utilisation was already low [19, 58, 179-182]. This contrasts with Poland where only limited activities have been undertaken to influence antibiotic utilisation. The lack of multifaceted approaches resulted in Poland continuing to have one of the highest rates of antibiotic consumption in Europe in recent years [183]. The impact of SAPG also mirrors the impact of multiple activities in England, including education, prescribing targets, and financial incentives, to reduce the prescribing of five broad-spectrum antibiotics (co-amoxiclav, ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin) in ambulatory care [184]. This multifaceted programme resulted in a 57% reduction in the prescribing of these five antibiotics; however, there was an increase in the number of isolates resistant to at least one of the five antibiotics suggesting additional programmes may still be needed [184]. The co-ordination of SAPG with other organisations in Scotland (**Table 1**) is in contrast to the situation seen in Namibia where different organisations were giving conflicting advice over different antimicrobials causing concern [185].

Multiple activities also enhanced the prescribing and dispensing of multiple sourced (generic medicines) at low prices versus originators. The situation in Scotland (Tables S1 and S2) contrasts with the impact of recent policies in South Korea. These policies had the opposite effect, with the ratio of originator to generic prescribing increasing without appropriate demand-side measures [186]. Consequently, simple and well thought out measures are usually needed to achieve desired goals rather than complex measures [186, 187]. Similarly in Abu Dhabi, the health authority introduced compulsory INN prescribing [188]. However, there were limited accompanying demand-side measures, resulting in physicians switching their prescribing to more expensive patented medicines in the class due to concerns with the quality of generics. Alongside this, limited controls over dispensing resulting in pharmacists dispensing a range of generics depending on factors including the extent of rebates from the different generic manufacturers. Consequently again, the envisaged savings were not realised in practice [188]. However, as mentioned, we are aware that the quality of generics can be concern in some countries, especially some LMICs, discouraging INN prescribing [41, 131, 132]. This needs to be addressed to enhance their use [152].

Multiple demand-side measures have also enhanced the preferential utilisation of low-cost multiple sourced medicines in other European countries [189, 190]. In Sweden, this resulted in expenditure on both PPIs and statins appre-

ciably decreasing between 2001 and 2007 despite significant increases in their utilisation [41, 189]. This was different to Ireland where the lack of demand-side measures resulted in increased utilisation of patented PPIs and statins following the availability of generics with a corresponding reduction in the prescribing of multiple sourced medicines. As a result, by the end of 2007, expenditure on both PPIs and statins in Ireland was over ten times that seen in Sweden when adjusted for population sizes [41, 189]. This mirrors the situation seen in Portugal with ACEIs and ARBs versus Scotland (**Table 2**). Encouragingly, multiple demand-side programmes in Scotland appeared to have a similar impact on limiting ARB utilisation as seen in Austria and Croatia, with both introducing prescribing restrictions (Enforcement) [46, 101]. This has important implications for countries such as Scotland where it is difficult to introduce prescribing restrictions [41]. These multiple activities also reduce the incentive for pharmaceutical companies to undertake evergreening activities to extend sales, with examples including esomeprazole versus omeprazole, escitalopram versus citalopram, and pregabalin versus gabapentin [153].

However, there were limited changes in the utilisation of losartan versus other ARBs in Scotland following the availability of generic losartan, with a conscious decision nationally and regionally not to influence its prescribing (**Table 2**). This mirrors the situation when the Better Care Better Value (BCBV) indicators were launched in the UK in 2009 to further enhance the preferential prescribing of multiple sourced ACEIs, which included potential therapeutic switching [191]. However, whilst there was a reduction in the rate of decline in the prescribing of ACEIs, the 80% BCBV target was not achieved [191]. A lack of comprehensive programmes including a lack of any financial incentive scheme, GPs already targeted for several years to limit ARB prescribing (**Table 2**), and a reluctance to instigate therapeutic switching despite studies showing no apparent negative impact [192, 193], may well have resulted in ACEI prescribing rates failing to reach target goals. This again suggests multiple and timely interventions are needed to appreciably influence physician prescribing. This is because we are aware of at least one Primary Care Group (PCG) in the UK which did instigate multiple demand-side measures to enhance the utilisation of generic losartan versus patented ARBs [145]. By the end of the multi-faceted programme, losartan accounted for 65% of all single ARBs in this PCG with annual net savings estimated at over eight-times the cost of implementation without compromising care [145].

We have seen that multiple measures have enhanced the prescribing of biosimilars without compromising care (**Table 3**). This is similar to the situation in Denmark where multiple measures resulted in the proportion of biosimilar adalimumab reaching 95.1% of total adalimumab by December 2018 and expenditure decreasing by 82.8% between September 2018 and December 2018 [103, 194]. This contrasts with limited use of biosimilar infliximab in South Korea with only limited price differences and limited demand-side measures [195].

Multiple approaches have also decreased the co-prescribing of medicines likely to increase AKI in the elderly across Scotland as well as the prescribing of sulfonylureas in the elderly (Section 3.5). However, this is not always the case as seen with limited success to date with multiple programmes to try and reduce the prescribing of anticholinergics and antipsychotics in the elderly. Consequently, additional measures may be needed to reach agreed targets as well as potentially involving a wider range of key stakeholders in this area of growing importance.

We are aware that there are a number of limitations. This includes the fact that we did not perform a systematic review, or give specific dates for the inclusion or exclusion of examples, since our goal was to provide exemplars rather that undertake a thorough review based on the considerable experiences of the co-authors. We also did not assess the quality of the papers using scales such as the Newcastle-Ottawa scale or the modified Jadad scale as our principal objective was again to provide guidance [196-199]. Despite these limitations, we believe we have documented robust examples across Scotland, and contrasted with other countries, to provide multiple exemplars of ways to improve the quality and efficiency of medicine use across disease areas and sectors. This also includes situations where initiatives did not work as expected.

Conclusion

Co-ordinated and integrated multiple interventions appear to have improved the quality and efficiency of medicine use across multiple disease areas and situations in Scotland. This ranges from integrated activities to better manage the entry and use of new medicines, through multiple activities to enhance appropriate antibiotic use, multiple sourced medicines and biosimilars. In addition, initiatives to tackle inappropriate polypharmacy. However, we are aware of situations where envisaged goals were not met. This calls for constant monitoring of medicine utilisation across sectors especially with the growth in expenditure on medicines in Scotland likely to be higher than the growth in healthcare spending generally in the coming years.

Disclosure of conflict of interest

A number of the co-authors are employed by the health service in Scotland. However, they have no other relevant conflicts of interest to declare.

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Table S1. % utilisation of multiple sourced oral medicines (generics) in Scotland

Class	Medicine	Generic utilisation as a % total utilisation for the medicine (DDD based or Items Dispensed)	Years (and reference)
Angiotensin converting enzyme inhibitors	Enalapril, Lisinopril	98-99%	2007 [46]
Angiotensin receptor blockers	Losartan	98%-99%	2010-2011 [154]
Antipsychotics	Risperidone	93% to 98%	2008 to 2010 [161]
Proton Pump Inhibitors	Esomeprazole	93.5% to 98%	2010 to 2017 [39]
	Lansoprazole	97.9% to 99%	2010 to 2017 [39]
	Omeprazole	96.7% to 99.1%	2010 to 2017 [39]
	Pantoprazole	87.3% to 100%	2010 to 2017 [39]
SSRIs	Citalopram	99.5%-99.9%	2010 to 2017 [38]
	Fluoxetine	98.7%-99.7%	2010 to 2017 [38]
	Paroxetine	91.4%-98.1%	2010 to 2017 [38]
	Sertraline	98.5%-99.7%	2010 to 2017 [38]
Statins	Atorvastatin	99.7%	2015 [40]
	Pravastatin	99.7%	2015 [40]
	Simvastatin	99.1%	2015 [40]

NB: DDD, defined daily dose, SSRIs, Selective Serotonin Reuptake Inhibitors. The ranges in generic utilisation rates for a number of the medicines reflect the minimum and maximum values during the studied years.

Box 1A. Examples in the UK where there are concerns with INN and brand name prescribing is encouraged (adapted from [41, 102, 200])

- Anti-epileptic drugs.
  - Including carbamazepine, phenytoin and primidone. The MHRA in the UK has advised GPs that patients should be maintained on specific treatments (Category 1) for these anti-epileptic treatments.
  - This is different to Category 3 anti-epileptic medicines such as levetiracetam, gabapentin and pregabalin where INN prescribing can take place unless there are specific reasons against INN prescribing such as patient anxiety [201].
- Treatments for respiratory diseases.
  - Theophylline modified release preparations.
  - Different inhalers for patients with asthma and COPD unless patients have the necessary knowledge and consent [44].
- Calcium antagonists-modified release preparations.
- Immunosuppressants, e.g. cyclosporin and mycophenolate mofetil-although cyclosporin is now less of a concern [202].
- Miscellaneous-Amphotericin intravenous, lithium, mesalazine, morphine sulphate slow-release tablets as well as fentanyl and nicotine transdermal patches.

NB: COPD, Chronic Obstructive Pulmonary Disease; INN, International non-proprietary name; MHRA, Medicines and Healthcare Products Regulatory Agency.

Table S2. % reduction in the reimbursed price of multiple sourced medicines in Scotland versus pre-patent originator prices

Class	Molecule	% price reduction for multiple sourced medicines versus pre-patent loss originator prices	Years (and reference)
Angiotensin converting enzyme inhibitors	Enalapril, Lisinopril	88%	2007 [46]
Angiotensin receptor blockers	Losartan	88%	2012 [154]
Antipsychotics	Risperidone	84%	2010 [161]
Oncology	Imatinib	89.1%	2018 [143]
Proton Pump Inhibitors	Esomeprazole	73.2%	2017 [39]
	Lansoprazole	90.1%	2017 [39]
	Omeprazole	91.5%	2017 [39]
	Pantoprazole	89.5%	2017 [39]
SSRIs	Citalopram	91.6%	2017 [38]
	Escitalopram	90.4%	2017 [38]
	Sertraline	91.8%	2017 [38]
Statins	Atorvastatin	92%	2015 [40]
	Pravastatin	92%	2015 [40]
	Simvastatin	95%	2015 [40]

NB: SSRIs, Selective Serotonin Reuptake Inhibitors. % reductions based on defined daily doses (DDDs), items dispensed or tablet prices depending on available DDDs and the rationale for the study.

Table S3. Multiple initiatives to enhance the prescribing of lower costs medicines in a class or related class and their outcomes

Medicine Class	Instigated Measures	Outcome
PPIs [39, 61]	● Education-Regional formularies advocating generic PPIs (e.g., omeprazole) following generic availability of both PPIs, which has continued. Educational initiatives to encourage the prescribing of lower dose PPIs (maintenance doses) to reduce potential adverse events and regular review of patients on long term PPIs especially those on polypharmacy and/or at risk of osteoporosis. ● Economics-Financial-based incentive schemes for primary care physicians to reach agreed targets including initially prescribing targets for generic vs. patented PPIs. ● Engineering-Agreed indicators to enhance the prescribing of generic vs. patented PPIs (withdrawn once the principal PPIs were available as generics); prescribing targets for esomeprazole when still patented, e.g., <4% of all PPI prescriptions; benchmarking potential savings from increased generic prescribing among physicians and Health Boards.	● These multiple measures resulted in total expenditure on PPIs 66.7% lower in Scotland in 2017 versus 2001 despite a 3.06-fold increase in utilization during this period. ● Appreciably increased utilisation of PPIs during their period was helped by high prevalence rates of dyspepsia in the community, concerns with growing admissions to hospitals due to GI bleeding, and the growing number of elderly patients in Scotland increasing the extent of polypharmacy and the associated potential for adverse reactions. ● There has been some reduction in the prescribing of higher strength PPIs in Scotland in recent years, which has been greater for higher strength omeprazole versus lansoprazole-currently the two most prescribed PPIs.

NB: PPIs, Proton pump inhibitors.

Box 1B. Recommended activities for addressing key issues with polypharmacy (adapted from [28])

1. Establishing a sense of urgency, e.g., communicating with key stakeholders the need for change and look at other projects that may pose a threat such as those evaluating cost-effectiveness without necessarily looking at concomitant safety implications.
2. Forming a powerful guiding coalition though e.g., assembling key stakeholders from across sectors as well as including national and regional Health Board personnel.
3. Creating a vision, e.g., outlining what any activities might do to improve future patient care.
4. Communicating the vision, e.g., through robust communication plans and face-to-face dialogue.
5. Empowering others to act on the vision, e.g., seek ways to enhance ownership of any plans produced to achieve desired objectives.
6. Planning for and creating short-term wins, e.g., identify projects to achieve this and share the results to foster enthusiasm in desired approaches.
7. Consolidating improvements and producing still more change, e.g., transferring projects to other areas to re-invigorate key personnel.
8. Institutionalise new approaches, e.g., sharing the benefits of activities with the organisation.

Table S4. Ongoing activities and guidance in Scotland to address concerns with polypharmacy in Scotland

Activity/Situation	Guidance
Criteria for prioritising patients for medication review [28]	Key criteria include: ● Patients aged 50 years or older and resident in a care home, regardless of the number of medicines prescribed. ● Patients approaching the end of their lives with risk versus benefit discussions often differing from healthy adults. As part of this, frailty scores should be considered (frailty considerations include multiple co-morbidities with signs of impairment in day to day functioning as well as a combination of at least three of the following: Weakness; slow walking speed; low physical activity; weight loss or self-reported exhaustion). ● Patients prescribed 10 or more medicines. ● Patients on high-risk medication regardless of the number of medicines being prescribed. If is not realistic to review all possible patients immediately, patients can be further stratified by: ● Age, e.g., 75 years and over, then 65 years and over. ● Frailty Scores (e.g., HIS Frailty/SPARRA score) - use the score which has been agreed by your organisation. ● Dominant condition including for instance dementia.
High risk medicines [28, 38, 39, 107]	Identified high risk medicines include: ● Positive inotropic medicines (Digoxin). ● Diuretics (including furosemide), medicines for hypertension/heart failure (Ramipril, enalapril, losartan). ● Anticoagulants and protamine including warfarin and DOACs as well as antiplatelet medicines including clopidogrel. ● Hypnotics and anxiolytics including benzodiazepines. ● Antipsychotic/antimanic drugs including amisulpride. ● Antidepressants including amitriptyline, paroxetine and citalopram. ● Opioid analgesics as well as medicines for rheumatic diseases and gout including NSAIDs, corticosteroids and methotrexate. ● Proton pump inhibitors (long term use/high doses).
The 7-Steps medication review [28, 45]	The seven steps are: ● Step 1: (Aim) What matters to the patient, e.g., identify aims and objectives of drug therapy by asking the patient what matters to the, explain key information and establishing treatment objectives with shared decision making. ● Step 2: (Need) Identify essential drug therapy, e.g., separating the list of medicines which the patient is taking and ensuring patients understand the importance of essential drug therapy. ● Step 3: (Need) Does the patient take unnecessary drug therapy, e.g. for the remaining drugs, it should be verified that each has a role and function in achieving desired therapeutic goals or outcomes and review preventative treatment to ensure the patient is able to continue taking prescribed medicines for the required time to gain benefit (to aid decision making the review contains a Drug Efficacy (NNT) table. ● Step 4: (Effectiveness) Are therapeutic objectives being achieved, e.g., treatment choices should be checked as the most effective to achieve intended outcomes including the potential need for dose titration (as recommended for e.g., PPIs). ● Step 5: (Safety) Is the patient at risk of ADRs or suffers actual ADRs, e.g., the presence of ADRs can sometimes be identified from laboratory data and patients must be encouraged to report ADRs or alternatively asked specific questions such as the presence of anticholinergic symptoms, dizziness or drowsiness. ● Step 6: (Efficiency) Is drug therapy cost-effective, e.g., what opportunities are there for cost minimisation should be explored as well as ensuring prescribing is in line with current formulary recommendations. ● Step 7: (Patient-Centred) Is the patient willing and able to take drug therapy as intended, e.g., does the patient understand the outcome of any medication review and ensure any drug therapy prescribed is tailored to patient preferences.

Sick-day rule guidance [28, 203]	● The sick-day rule guidance was developed as a resource for patients, carers and health professionals to promote better management of long-term conditions, with the cards patients receive highlighting the potential harm which can be caused if they continue to take certain medicines whilst suffering from illnesses where dehydration can occur. ● The Sick Day Medicine rules includes advice to patients to stop taking medicines ticked on cards provided by health professionals when feeling unwell with vomiting, diarrhoea, fevers, sweats and shaking and restart when well. ● Key medicines include: ACEIs, ARBs, diuretics, metformin and NSAIDs.
Development of 69 *Case Finding* prescribing and monitoring indicators [28, 204]-developed into Quality Indicators [205]	27 indicators develop which utilise patient level prescribing data (PIS) and include: ● Cardiac decompensation and/or bradycardia. ● Bleeding, e.g., prescribed aspirin and another antiplatelet without gastroprotection. ● Bone Marrow Suppression, e.g., patients prescribed methotrexate without folic acid or with long-term trimethoprim. ● Acute Kidney Injury, e.g., patients prescribed an ACEI/ARB along with a diuretic and NSAID. ● Hyperkalaemia, e.g., patients prescribed ACEI/ARB and a potassium supplement. ● Hypoglycaemia, e.g., patients prescribed insulin without concomitant glucose test strips. ● Falls, Fractures and Delirium, e.g., patients prescribed steroids long term without co-prescription of a bone protecting agent. ● Opioids and gabapentinoid dependency, e.g., patients prescribed opioid at doses equivalent to >180 mg morphine per day over last 6 months. ● Seizures and neurotoxicity, e.g., patients on lithium prescribed an NSAID. ● Extrapyramidal symptoms, e.g., patients prescribed levodopa and metoclopramide long term. The remaining 42 *Case Finding* indicators utilise diagnosis, examination signs and laboratory data and grouped as *Composite* indicators to help linkage with other clinical diagnosis data sets such as hospital admission data. Disease areas/conditions include: Cardiac decompensation and/or bradycardia; Bleeding; Bone Marrow Suppression; Acute Kidney Injury; Hyperkalaemia; Hypokalaemia; Hyponatraemia; Hypercalcaemia; Hypocalcaemia; Hypoglycaemia and Lactic Acidosis; Hypotension; Stroke/Vascular Events; Respiratory Exacerbation; Falls, fractures and delirium; Opioid and gabapentinoid dependency; Seizures and neurotoxicity; Extrapyramidal Symptoms and Gynaecological Cancer.
The Scottish Therapeutics Utility (STU) Computer Programme [206]	STU is a computer programme that interrogates data from General Practice IT systems that enables GPs and Health Board Pharmacy Advisers to focus on key prescribing areas including repeat prescribing and high risk prescribing incorporating unnecessary polypharmacy.

NB: ACEIs, angiotensin converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; PPIs, Proton pump inhibitors; NSAIDs, Non-steroid anti-inflammatory drugs.