Title: Prescriber implementation of STOPP/START recommendations for hospitalised older adults: a comparison of a pharmacist approach and a physician approach

Kieran Dalton [a], Denis O'Mahony [b, c], David O'Sullivan [a], Marie N. O'Connor [c], Stephen Byrne [a]

[a] Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland.

[b] Department of Medicine, University College Cork, Cork, Ireland.

[c] Geriatric Medicine, Cork University Hospital, Cork, Ireland.

Corresponding author e-mail address: k.a.dalton@umail.ucc.ie and stephen.byrne@ucc.ie

Running title: Prescriber implementation of STOPP/START recommendations: pharmacist approach versus physician approach

Abstract

Background

Two randomised controlled trials (RCTs) conducted simultaneously in the same Irish university teaching hospital have shown that provision of STOPP/START recommendations to attending prescribers by a physician or a pharmacist can reduce in-hospital adverse drug reactions (ADRs) in older adults (≥ 65 years). The aims of this study were to compare the prescriber implementation rates of STOPP/START recommendations between the physician approach and the pharmacist approach in these two RCTs, and to provide a narrative summary of the comparable clinical outcomes.

Methods

Data were extracted from the two RCT published papers and their associated computerised databases to calculate the percentage (%) prescriber implementation rates for the STOPP/START recommendations. The chi-square test was used to quantify the differences in prescriber implementation rates, with differences considered statistically significant where $p < 0.05$.

Results

Prescriber implementation rates of the STOPP and START recommendations made by the physician were 81.2% and 87.4% respectively, significantly higher than those made by the pharmacist (39.2% and 29.5% respectively), $p < 0.0001$. A greater absolute risk reduction in patients with ADRs was shown with the physician's intervention compared to the pharmacist's intervention (9.3% versus 6.8%).

Conclusion

This study shows that the methods of communication and the medium through which the STOPP/START recommendations are delivered significantly affect their implementation. Non-implementation of some pharmacist-delivered recommendations may be contributing to preventable ADRs in older adults. Thus, future research should aim to identify the factors influencing prescriber

implementation of pharmacist recommendations in order to inform the design of more effective pharmacist interventions in optimising older patients' pharmacotherapy.

Key points

- Prescribers were significantly more likely to implement STOPP/START recommendations from one physician approach compared to one pharmacist approach in this Irish university teaching hospital ($p < 0.0001$).

- Increased implementation of the physician's recommendations may have been an important factor in preventing a larger proportion of in-hospital ADRs in comparison to the pharmacist's intervention. However, cost-effectiveness analyses of these interventions would suggest that only the pharmacist's intervention was cost-effective.

- Future research should aim to identify the barriers and facilitators to prescriber implementation of hospital pharmacist recommendations so as to inform the design of more effective pharmacist interventions which target pharmacotherapy optimisation in multi-morbid older adults.

Word Count: 3,689

Number of References: 35

Number of Tables: 2 (plus 3 in Supplementary Data)

Number of Figures: 0

1. INTRODUCTION

Potentially inappropriate prescribing (PIP) in multi-morbid older adults continues to be a major healthcare problem worldwide. PIP encompasses the prescription of potentially inappropriate medications (PIMs), mis-prescribing (e.g. an inappropriate frequency, dose, or duration), or the failure to prescribe medications that would likely benefit patients, so-called potential prescribing omissions (PPOs). Previous studies have demonstrated that PIP is one of the primary causes for adverse drug reactions (ADRs) in older adults [1, 2]. Identifying PIP instances that could increase the risk of ADRs is important and, where possible, alternatives should be considered that may be equally effective with a lower risk of harm to older patients [3]. STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria are well recognised as tools for identifying PIP instances in older people across multiple healthcare settings [4].

Two recently published randomised controlled trials (RCTs) conducted in the same large university teaching hospital in southern Ireland demonstrated a clinically significant absolute risk reduction in incident ADRs in multi-morbid older adults arising from physician-delivered and pharmacist-delivered pharmacotherapy recommendations to attending prescribers [5, 6]. Both RCTs included the primary researcher (physician or pharmacist) providing recommendations based on STOPP/START criteria version 1 [7] to attending physician prescribers caring for hospitalised older adults.

The primary aim of this study was to compare the prescriber implementation rates of STOPP and START recommendations from these two RCTs conducted simultaneously in the same Irish university teaching hospital, where the recommendations were delivered by a physician in one trial and by a pharmacist in the other trial [5, 6]. Secondary aims were to identify components within the interventions that may have affected prescriber implementation, to compare the prescriber implementation of the pharmacist's STOPP/START recommendations with other pharmacist-delivered recommendations, and to provide a narrative summary of comparable clinical outcomes in the two RCTs.

2. METHODS

2.1 Study setting and intervention details

Both RCTs were conducted in Cork University Hospital, an 810-bed tertiary referral centre in southern Ireland. Participants were enrolled within 48 hours of their presentation to hospital with acute illness. The interventions in both RCTs primarily aimed to reduce non-trivial in-hospital ADRs in older adults ($\geq$ 65 years), and are briefly summarised as follows:

In both RCTs [5, 6], the primary researcher applied the STOPP/START criteria (version 1) [7] at a single time point to the medication list of intervention patients within 48 hours of hospital admission, and placed a printed report in the patient's clinical records with STOPP/START-based recommendations. The primary researcher verbally notified the attending prescribers of the recommendations and answered any clarifying questions that they may have had.

In RCT 1, the physician verbally notified the attending prescribers of the STOPP/START-based recommendations for all patients [5]; in RCT 2, the pharmacist verbally notified the attending prescribers of the recommendations for approximately one third of patients, but provided mobile phone contact details on the printed report in case prescribers wanted verbal clarification on the pharmacist's advice [6]. In RCT 2, the pharmacist's STOPP/START-based recommendations were provided in conjunction with recommendations based on other medication appropriateness issues, i.e. including drug-drug interactions, need for renal and hepatic dose adjustments, and other PIP instances identified utilising Beers criteria (version 3) [7] and PRISCUS criteria [8], as well as issues based on medication reconciliation, which has been defined as the "process of identifying the most accurate list of all medications a patient is taking - including name, dosage, frequency, and route - and using this list to provide correct medications for patients anywhere within the health care system" and "involves comparing the patient's current list of medications against the physician's admission, transfer, and/or discharge orders" [9]. The medication reconciliation issues in RCT 2 were primarily due to medications omitted and incorrect doses prescribed on admission [10]. In RCT 1, the physician was a specialist registrar (senior resident) in geriatric medicine with 3 years of specialist clinical experience [5]. In RCT

2, the pharmacist was fully registered with 4 years of postgraduate experience in providing pharmaceutical care to older adults.

Both trials used a cluster randomised design. In each RCT, two lists of attending consultant prescribers were created such that the combined rates of ADRs in these groups were known to be comparable from previous work undertaken by this group [11]. Having finalised the lists, one group of attending consultant prescribers was assigned as the intervention arm of the study and the other was assigned as the control arm. The intervention clusters in both RCT 1 and RCT 2 included individuals admitted under the care of specialists in cardiology, respiratory medicine, endocrinology, renal medicine, and orthopaedics. The intervention cluster in RCT 1 also consisted of patients admitted under the care of specialists in radiation oncology, whilst the intervention cluster in RCT 2 also included patients admitted under the care of specialists in rheumatology, general and vascular surgery, and general internal medicine. To avoid potentially biased enrolment of patients into either arm of the study, the primary researcher in each RCT approached prospective trial participants in the order of their admission to the hospital's emergency department to assess their eligibility for the trial. RCT 1 was conducted from May 2011 to May 2012. RCT 2 was conducted from June 2011 to July 2012. No patient in either RCT received the intervention from the other RCT. Patients in the intervention and control groups in both RCTs received standard medical and pharmaceutical care from physicians and pharmacists who routinely work in the hospital. Implementation of recommendations was assessed by the primary researcher of each trial at day 7-10 or at the point of hospital discharge (whichever came first). Further details (e.g. such as study design and patient characteristics) can be found in the published papers describing these RCTs [5, 6, 10].

2.2 Data Extraction and Analysis

As part of this secondary data analysis, data were extracted from the papers based on the RCTs [5, 6, 10], and their associated computerised databases, stored locally in Microsoft® Access. The percentage (%) prescriber implementation rates for the STOPP and START recommendations were calculated for both RCTs. The chi-square test was used to compare the prescriber implementation rates of the STOPP

and START recommendations in the pharmacist and physician intervention groups, as well as to quantify any differences between the implementation of STOPP/START recommendations and other recommendations included in the pharmacist's intervention. Differences were considered statistically significant where $p < 0.05$.

3. RESULTS

3.1 Prescriber Implementation of STOPP and START recommendations

Tables 1 and 2 show the prescriber implementation rates of STOPP and START recommendations from the physician and pharmacist respectively, divided according to the relevant physiological systems.

In 360 intervention patients in RCT 1, the physician made 292 STOPP recommendations (0.81/patient) and 159 START recommendations (0.44/patient) i.e. a total of 1.25 STOPP/START recommendations per patient. Attending prescribers implemented 237 of the physician's 292 STOPP recommendations (81.2%) and 139 of the physician's 159 START recommendations (87.4%). In 361 intervention patients in RCT 2, the pharmacist made 255 STOPP recommendations (0.71/patient), and 44 START recommendations (0.12/patient) i.e. a total of 0.83 STOPP/START recommendations per patient. Attending prescribers implemented 100 of the pharmacist's 255 STOPP recommendations (39.2%) and 13 of the pharmacist's 44 START recommendations (29.5%).

In total, attending prescribers implemented 83.4% of the physician's STOPP/START recommendations (376/451) compared to 37.8% of the pharmacist's STOPP/START recommendations (113/299). When comparing the physician and pharmacist interventions, there was a statistically significant difference between prescriber implementation rates of the total STOPP, total START, and total STOPP/START-combined recommendations ($p < 0.0001$).

Of the ten categories of STOPP criteria, recommendations were made by both physician and pharmacist across eight of these categories. The physician achieved higher implementation rates than the pharmacist for recommendations across all eight STOPP categories, with the absolute differences

ranging from 11.1% to 55.5%. The largest absolute difference observed was for recommendations based on the gastrointestinal system. This was primarily due to the low implementation rate of pharmacist recommendations to deprescribe PPIs (38/115), which was the most common type of STOPP/START recommendation provided in both RCTs. There were statistically significant differences in the implementation rates of recommendations across six of the eight STOPP categories, with the exceptions being recommendations based on urogenital system drugs and analgesic drugs. Of the six categories of START criteria, recommendations were made by both physician and pharmacist across three of these categories. The physician achieved statistically significantly higher implementation rates than the pharmacist for recommendations across all three START categories, with the absolute differences ranging from 51.7% to 70%.

Of the 65 individual STOPP criteria, recommendations based on 22 of these were prevalent in both RCTs. The physician achieved higher implementation rates than the pharmacist for recommendations based on 19 of these 22 STOPP criteria, for which statistically significant differences were observed for 7 of these 19 STOPP recommendations, as shown in Table 1. The pharmacist achieved a higher implementation rate than the physician for recommendations based on one of the STOPP criteria – STOPP rule A8: "Calcium channel blockers with chronic constipation (*may exacerbate constipation*)" - but this difference was not statistically significant (9/11 versus 2/4; $p = 0.2178$). Of the 22 individual START criteria, recommendations based on 8 of these criteria were prevalent in both RCTs. The physician achieved higher implementation rates than the pharmacist for recommendations linked to 6 of these 8 START criteria, for which statistically significant differences were observed for 3 of these 6 START recommendations, as shown in Table 2. The pharmacist achieved a higher implementation rate than the physician for recommendations based on one of the START criteria – START rule A3: "Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm"; once again, this difference was not statistically significant (2/5 versus 0/2; $p = 0.2899$).

3.2 Number of recommendations made and focus of intervention

Of the 360 patients randomised to the intervention arm in RCT 1, the physician made 451 recommendations in 233 patients (1.94 recommendations per patient). Of the 361 patients randomised to the intervention arm in RCT 2, the pharmacist made 1000 recommendations in 296 patients (3.38 recommendations per patient). Thus, for patients where pharmacotherapy recommendations were provided, the pharmacist provided 1.44 more recommendations per patient in comparison to the physician.

In RCT 2, the pharmacist's STOPP/START recommendations represented almost 30% of the total number of recommendations (299/1000), and 51.8% (299/577) of the medication appropriateness recommendations (i.e. including drug-drug interactions, need for renal and hepatic dose adjustments, and other PIP instances identified utilising Beers criteria (version 3) [7] and PRISCUS criteria [8]) [10]. The remainder of the pharmacist's recommendations concerned issues with medication reconciliation (n = 423), of which 326 were implemented (77.1%). The implementation rate of the pharmacist's recommendations concerning medication reconciliation recommendations was approximately double the rate of those concerning STOPP/START criteria (77.1% versus 37.8%; $p < 0.0001$).

3.3 Pharmacist Medication Reconciliation recommendations based on START criteria

On initial viewing of the START recommendations in both RCTs, it is evident that the physician made 3.67 times more START recommendations per patient in RCT 1 compared to the pharmacist in RCT 2 (0.44 START/patient versus 0.12 START/patient). The physician did not conduct medication reconciliation, whereas the pharmacist did. Therefore, as part of the pharmacist's intervention, there were 322 recommendations to prescribe "*missing medications*" (i.e. medications that were prescribed prior to admission but omitted from the patient's list of medications on admission), of which 71 (22.0%) would have been identified by the START criteria based on the patients' lists of prescribed medications on admission and comorbidities (as shown in Appendix 1). Fifty-eight of these recommendations were implemented (81.7%). Prescribers were therefore substantially more likely to implement a recommendation from a pharmacist to initiate a START criteria-based drug if it had previously been

prescribed by a physician rather than based on the pharmacist's recommendation alone (81.7% versus 29.5%; $p < 0.0001$).

If the 71 recommendations to prescribe START criteria-based "*missing medications*" were factored in to the comparison between implementation of physician-delivered and pharmacist-delivered STOPP/START recommendations (Appendix 2), the physician would still achieve statistically significantly higher implementation rates for:

(a) the total START recommendations: 139/159 (87.4%) versus 71/115 (61.7%); $p < 0.0001$, and

(b) the total STOPP/START recommendations: 376/451 (83.4%) versus 171/370 (46.2%); $p < 0.0001$.

3.4 Clinical Outcomes

The comparable clinical outcomes from the two RCTs are displayed in Appendix 3. The physician's intervention resulted in an absolute reduction of 9.3% in the proportion of patients who experienced a non-trivial in-hospital ADR in comparison to the control group, compared to the pharmacist's intervention which resulted in an absolute reduction of 6.8% for this same outcome. The corresponding relative risk reductions for this outcome were 44.3% and 32.9% respectively. Neither intervention resulted in significant differences in median length of hospital stay or mortality when compared to controls.

4. DISCUSSION

There is a paucity of research comparing pharmacists and physicians in the provision of pharmacotherapy recommendations in hospitalised older adults. This is the first study to compare prescriber implementation rates of STOPP/START recommendations from one approach by a trained clinical pharmacist with another approach by a physician trained in geriatric medicine. Our results have shown that the source of the STOPP/START recommendations and the communication methods

through which they are provided may have a substantial impact on their implementation. We found that physician prescribers in this particular hospital in southern Ireland were statistically significantly more likely to implement STOPP/START recommendations from the physician's approach and delivery than from the pharmacist's in these two RCTs. There was a greater disparity between the two approaches in the implementation of START recommendations (87.4% versus 29.5%) compared to the implementation of STOPP recommendations (81.2% versus 39.2%).

A small sample size may have prevented showing statistically significant differences in the prescriber implementation rates of certain STOPP or START recommendations between physician and pharmacist. Nevertheless, our study has demonstrated that the physician obtained statistically significantly higher implementation rates than the pharmacist for 10 of the 30 individual STOPP/START recommendations present in both interventions, including recommendations to deprescribe benzodiazepines and proton pump inhibitors. In recent years, there has been extensive research on deprescribing of these drugs in particular [12-14]. The present study is consistent with previous findings that geriatricians may be more effective than other healthcare professionals with deprescribing in hospitalised older adults [14, 15].

The authors recognise that differences between the interventions, other than the individual healthcare professionals, may have had an influence on prescriber implementation rates, such as:

- The pharmacist provided other recommendations, not just STOPP/START recommendations as the physician did.
- Both the pharmacist and physician provided all of the recommendations in written form. The physician also communicated all recommendations verbally, whereas the pharmacist verbally communicated approximately one third of these recommendations.
- The physician had previously worked in the hospital prior to RCT commencement, whereas the pharmacist had not.

The physician-delivered intervention was narrowly focused on providing recommendations based on the STOPP/START criteria only, whereas the pharmacist's intervention involved the provision of

recommendations based on STOPP/START as well as a wider range of drug-related problems. As previously stated, the pharmacist provided 1.44 more recommendations on average per patient than the research physician to attending prescribing teams. A recent systematic review suggests that computerised interventions which target a broader range of PIP issues in older adults may contribute to information overload, and consequently result in fewer recommendations being implemented [16]. Thus, in the present study, the greater complexity of the pharmacist intervention compared to the physician intervention may have resulted in a lower implementation rate of pharmacotherapy recommendations by attending prescribers.

Previous studies have shown that pharmacists and physicians prefer the use of verbal or face-to-face recommendations when working in collaboration to review pharmacotherapy [17, 18]. Recommendations communicated in this way are usually implemented at a higher rate than those provided by written means alone [19-22]. This suggests that the pharmacist might have achieved higher implementation rates if he had provided verbal reinforcement to prescribers regarding all the recommendations in the printed report. However, the high implementation rate of the pharmacist's medication reconciliation recommendations (77.1%) suggests that the mode of delivery of the pharmacist's recommendations may not have been the primary cause of the observed difference in STOPP and START recommendation implementation rates between the pharmacist and physician. Moreover, the contrast in implementation between pharmacist medication reconciliation recommendations and STOPP/START recommendations is noteworthy. This difference suggests that there may be an impediment to prescriber implementation of pharmacist interventions relating to prescribing appropriateness in older patients, and that physicians may be more accepting of the pharmacist's role in medication reconciliation as distinct from prescribing alterations.

Both the pharmacist and the physician were highly familiar with the STOPP/START criteria prior to the start of the two RCTs. Previous studies have demonstrated that inter-rater reliability amongst pharmacists and physicians is high when provided with the same clinical information [23, 24]. Therefore, identification of PIP by either healthcare professional should not have been different. A key factor in achieving implementation of prescribing recommendations may be *who* provides them, and

how they are delivered to prescribers. Physicians may be more likely to implement recommendations from fellow physicians, as this is customary practice in healthcare systems worldwide. Physicians may be less likely to implement pharmacist recommendations but the reasons for this are not fully understood. A qualitative study by Hughes *et al* [25] found that some pharmacists felt that doctors considered them to be subordinate on a professional level in relation to medication issues. In that study, hierarchical differences were implicit in the doctors' comments as they questioned the role of pharmacists in certain areas, such as having greater involvement with prescribing decisions, which some doctors viewed to be solely within the professional domain of the doctor. The same study suggested that this may be because of some doctors' lack of awareness of pharmacist training, as well as some doctors feeling that greater pharmacist involvement would encroach on their prescribing role. Most of the studies in this area of research are focused on the relationships between pharmacists and physicians in primary care, and there appears to be limited research into exploring the factors affecting physician implementation of pharmacist recommendations in secondary care settings [25-27].

Prior to commencement of the RCTs, the research physician had previously worked in the same hospital training in geriatric medicine at specialist registrar (senior resident) level. As a result, this particular physician may have already established a good professional rapport with some of the attending prescribers prior to RCT 1. This, in turn, may have contributed to an increased implementation of the STOPP/START recommendations offered by the research physician. In contrast, whilst the research pharmacist was experienced in providing pharmaceutical care for older adults, he had not previously worked in the hospital where the RCTs were conducted. Previous research has highlighted that key components to physician-pharmacist collaboration are trust and 'knowing' each other [28], and that pharmacists who work closely with physicians are more likely to be successful in optimising geriatric pharmacotherapy [29]. These inter-professional barriers may have contributed to the observed lower implementation rate of the pharmacist's STOPP/START recommendations described in this study.

Published studies providing details on prescriber implementation of pharmacist and physician STOPP/START recommendations are limited. An earlier RCT conducted by a physician in the same hospital (where medication appropriateness was the primary outcome measure) demonstrated a very

high level of prescriber implementation of both the STOPP (91%) and START (97%) recommendations [30]. Although this intervention took place in the hospital where the STOPP/START criteria were developed, it is unlikely that this is the reason for the high implementation rates as the criteria are not routinely applied to older patients there due to resource constraints. The implementation rates of the pharmacist's STOPP and START recommendations in this present study seem to be lower than those described in the literature to date (STOPP: 44% – 94% and START: 58%) [31, 32]. Therefore, our results support previous findings which indicate that a lower proportion of pharmacist-provided STOPP/START recommendations are implemented by prescribers in comparison to those provided by physicians.

There are some limitations to this study. Firstly, although both the original pharmacist and physician interventions encompass STOPP and START recommendations, they were not designed to be directly compared. Differences between the interventions cannot be ruled out as possible contributing factors to the difference in outcomes observed. Secondly, this was a single-centre comparison between the prescriber implementation rates of recommendations provided by one pharmacist and one physician. Evaluating implementation of STOPP and START recommendations from a larger sample of pharmacists and physicians in a multi-centre RCT setting would provide a more accurate comparison of the professions on this matter, as we recognise that different personalities and communication styles also vary between individuals, which may impact on the implementation rates.

A cost-effectiveness analysis of the pharmacist intervention has shown that it was cost-effective [33]. However, a more recent cost-effectiveness analysis indicates that the physician intervention was unlikely to be cost-effective [34], even though it was associated with a greater absolute risk reduction in patients with ADRs compared to the pharmacist intervention. The present study suggests that a higher prescriber implementation rate of STOPP recommendations in particular is associated with lower rates of incident ADRs in hospitalised older adults. Therefore, it could be argued that the lower implementation rate of some of the pharmacist's recommendations resulted in a higher rate of incident ADRs in the pharmacist RCT intervention cohort. Previous studies have consistently shown that pharmacists contribute to reductions in healthcare costs in the hospital setting [35]. If physicians are

less likely to be cost-effective in conducting interventions of this type, it is important that other ways to enhance the implementation of pharmacist recommendations are identified, which reliably lead to further reductions in ADRs, and subsequently lower healthcare costs.

5. CONCLUSION

This study shows that the methods of communication and the medium through which the STOPP/START recommendations are provided may have a significant impact on their implementation. Qualitative research is necessary to identify the key factors affecting prescriber implementation of hospital pharmacist recommendations, along with possible ideas for future intervention, as non-implementation of these recommendations probably contribute to preventable ADRs occurring in hospitalised older adults.

Compliance with Ethical Standards

Funding

Kieran Dalton and Denis O'Mahony were funded by the SENATOR project, supported by the Seventh Framework Programme FP7/2007-2013 under grant agreement number 305930. David O'Sullivan and Marie N. O'Connor were funded by a Health Research Board of Ireland grant to conduct the original

RCTs (Grant HRA_HSR/2010/14). The funders had no part in the design of this study, the collection, analysis and interpretation of the data, the writing of the report, or the decision to submit the article for publication.

Conflicts of interest

Stephen Byrne and Denis O'Mahony have part ownership in a patent "A Prescription Decision Support System" (based on STOPP/START prescribing rules); the patent was registered with the European Patent Office (Munich); Patent no. 11757950.8– 1952. Stephen Byrne and Denis O'Mahony are also affiliated with two European Commission-funded grants that involve clinical trials in which there is computerised deployment of the STOPP/START criteria as part of an intervention designed to optimise pharmacotherapy in older adults. The first European Commission grant is called "Development and clinical trials of a new Software ENgine for the Assessment and Optimization of drug and non-drug Therapy in Older peRsons [SENATOR]", grant agreement 305930, awarded under the Seventh Framework Programme (FP7). The trial is registered with the US National Institutes of Health (NCT02097654). Denis O'Mahony is coordinator of the SENATOR project. The second European Commission-funded project is called "OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly". OPERAM is funded under the Horizon 2020 programme (PHC 17- 2014). The OPERAM trial is based on another software intervention called "Screening Tool to Reduce Inappropriate Prescribing", which uses STOPP/START rules to assess the pharmacotherapy of older people. The trial is registered with the US National Institutes of Health (NCT02986425). Kieran Dalton, David O'Sullivan, and Marie N. O'Connor have no conflicts of interest that are directly relevant to the content of this article.

Ethical approval

Both RCTs were approved by the research ethics committee of the local teaching hospitals network, and both were registered with the National Institutes of Health in the United States: ClinicalTrials.gov identifier for RCT 1: NCT01467050; ClinicalTrials.gov identifier for RCT 2: NCT01467128. Written consent was obtained from all participating patients (or their next of kin) prior to RCT enrolment.

REFERENCES

1. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. Drugs & aging. 2005;22(9):767-77.

2. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Archives of internal medicine. 2011 Jun 13;171(11):1013-9.

3. Opondo D, Eslami S, Visscher S, de Rooij SE, Verheij R, Korevaar JC, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. PloS one. 2012;7(8):e43617.

4. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. Journal of clinical pharmacy and therapeutics. 2013 Oct;38(5):360-72.

5. O'Connor MN, O'Sullivan D, Gallagher PF, Eustace J, Byrne S, O'Mahony D. Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial. Journal of the American Geriatrics Society. 2016 Aug;64(8):1558-66.

6. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Gallagher J, Cullinan S, et al. Prevention of Adverse Drug Reactions in Hospitalised Older Patients Using a Software-Supported Structured Pharmacist Intervention: A Cluster Randomised Controlled Trial. Drugs & aging. 2016 Jan;33(1):63-73.

7. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Archives of internal medicine. 2003 Dec 8-22;163(22):2716-24.

8. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Deutsches Arzteblatt international. 2010 Aug;107(31-32):543-51.

9. Resar R, Midelfort L. Medication reconciliation review. Boston: Institute for Healthcare Improvement. 2004.

10. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R, et al. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs & aging. 2014 Jun;31(6):471-81.

11. O'Connor MN, Gallagher P, Byrne S, O'Mahony D. Adverse drug reactions in older patients during hospitalisation: are they predictable? Age and ageing. 2012 Nov;41(6):771-6.

12. Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. European journal of clinical pharmacology. 2017 Aug;73(8):927-35.
13. Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. The British journal of psychiatry : the journal of mental science. 2014 Feb;204(2):98-107.
14. Wilsdon TD, Hendrix I, Thynne TR, Mangoni AA. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs & aging. 2017 Apr;34(4):265-87.
15. Lang PO, Vogt-Ferrier N, Hasso Y, Le Saint L, Drame M, Zekry D, et al. Interdisciplinary geriatric and psychiatric care reduces potentially inappropriate prescribing in the hospital: interventional study in 150 acutely ill elderly patients with mental and somatic comorbid conditions. Journal of the American Medical Directors Association. 2012 May;13(4):406.e1-7.
16. Dalton K, O'Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. Age and ageing. 2018 Jun 8.
17. Snyder ME, Zillich AJ, Primack BA, Rice KR, Somma McGivney MA, Pringle JL, et al. Exploring successful community pharmacist-physician collaborative working relationships using mixed methods. Research in social & administrative pharmacy : RSAP. 2010 Dec;6(4):307-23.
18. Bergman AA, Jaynes HA, Gonzalvo JD, Hudmon KS, Frankel RM, Kobylinski AL, et al. Pharmaceutical Role Expansion and Developments in Pharmacist-Physician Communication. Health communication. 2016;31(2):161-70.
19. Lessard S, DeYoung J, Vazzana N. Medication discrepancies affecting senior patients at hospital admission. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2006 Apr 15;63(8):740-3.
20. Pound MW, Miller SM. Written versus oral recommendations made by pharmacy students during internal medicine rotations. The Annals of pharmacotherapy. 2007 May;41(5):772-6.

21. Rigby D. Collaboration between doctors and pharmacists in the community. Australian Prescriber. 2010 Dec;33(6):191-3.
22. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. Comparison of two methods for performing treatment reviews by pharmacists and general practitioners for home-dwelling elderly people. Journal of evaluation in clinical practice. 2008 Jun;14(3):446-52.
23. Gallagher P, Baeyens JP, Topinkova E, Madlova P, Cherubini A, Gasperini B, et al. Inter-rater reliability of STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria amongst physicians in six European countries. Age and ageing. 2009 Sep;38(5):603-6.
24. Ryan C, O'Mahony D, Byrne S. Application of STOPP and START criteria: interrater reliability among pharmacists. The Annals of pharmacotherapy. 2009 Jul;43(7):1239-44.
25. Hughes CM, McCann S. Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment. The British journal of general practice : the journal of the Royal College of General Practitioners. 2003 Aug;53(493):600-6.
26. Bechet C, Pichon R, Giordan A, Bonnabry P. Hospital pharmacists seen through the eyes of physicians: qualitative semi-structured interviews. International journal of clinical pharmacy. 2016 Dec;38(6):1483-96.
27. Rubio-Valera M, Jove AM, Hughes CM, Guillen-Sola M, Rovira M, Fernandez A. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. BMC health services research. 2012 Jul 7;12:188.
28. Bradley F, Ashcroft DM, Noyce PR. Integration and differentiation: a conceptual model of general practitioner and community pharmacist collaboration. Research in social & administrative pharmacy : RSAP. 2012 Jan-Feb;8(1):36-46.
29. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet (London, England). 2007 Jul 14;370(9582):173-84.

30. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clinical pharmacology and therapeutics. 2011 Jun;89(6):845-54.

31. Hannou S, Voirol P, Pannatier A, Weibel ML, Sadeghipour F, von Gunten A, et al. Pharmacist intervention acceptance for the reduction of potentially inappropriate drug prescribing in acute psychiatry. International journal of clinical pharmacy. 2017 Dec;39(6):1228-36.

32. Kimura T, Ogura F, Yamamoto K, Uda A, Nishioka T, Kume M, et al. Potentially inappropriate medications in elderly Japanese patients: effects of pharmacists' assessment and intervention based on Screening Tool of Older Persons' Potentially Inappropriate Prescriptions criteria ver.2. Journal of clinical pharmacy and therapeutics. 2017 Apr;42(2):209-14.

33. Gallagher J, O'Sullivan D, McCarthy S, Gillespie P, Woods N, O'Mahony D, et al. Structured Pharmacist Review of Medication in Older Hospitalised Patients: A Cost-Effectiveness Analysis. Drugs & aging. 2016 Apr;33(4):285-94.

34. O'Brien GL, O'Mahony D, Gillespie P, Mulcahy M, Walshe V, O'Connor MN, et al. Cost-Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland. Drugs & aging. 2018 July 13.

35. Dalton K, Byrne S. Role of the pharmacist in reducing healthcare costs: current insights. Integrated pharmacy research & practice. 2017;6:37-46.

Table 1: Prescriber Implementation Rates for STOPP Recommendations: Physician versus Pharmacist

STOPP criteria	Physician	Pharmacist	*p*-value
Cardiovascular System	**22/26 (84.6%)**	**14/26 (53.9%)**	**0.0162***
Digoxin at a long-term dose > 125micrograms per day with impaired renal function	1/1	-	-
Loop diuretic for dependent ankle oedema only	4/6	1/2	0.6733
Loop diuretic as first- line monotherapy for hypertension	4/4	0/1	0.0253*
Non-cardioselective beta-blocker with COPD or asthma	9/9	2/7	0.0022*
Beta-blocker in combination with verapamil	1/1	-	-
Calcium channel blockers with chronic constipation	2/4	9/11	0.2178
Use of aspirin and warfarin in combination without histamine H_2 receptor antagonist or proton pump inhibitor (high risk of gastrointestinal bleeding)	-	1/4	-
Aspirin at dose > 150mg day	-	1/1	-
Aspirin without coronary, cerebral or peripheral arterial symptoms or occlusive arterial event	1/1	-	-
Central Nervous System	**37/46 (80.4%)**	**15/33 (45.5%)**	**0.0012***
Tricyclic antidepressants with dementia	3/3	-	-
Tricyclic antidepressants with glaucoma	1/1	-	-
Tricyclic antidepressants in chronic constipation	3/3	3/4	0.3496
Tricyclic antidepressants in combination with an opiate or calcium channel blocker	1/1	6/8	0.5708
Long-term (>1month) use of long-acting benzodiazepines	16/25	4/16	0.0148*
Long-term (>1 month) use of neuroleptics as hypnotics	4/4	-	-
Long-term (>1 month) use of neuroleptics in those with parkinsonism	2/2	1/1	‡
Phenothiazines in patients with epilepsy	-	0/1	-
SSRIs with a history of clinically significant hyponatraemia	5/5	1/1	‡
Prolonged use (>1week) of 1st generation antihistamines	2/2	0/2	0.0455*
Gastrointestinal System	**85/96 (88.5%)**	**39/118 (33%)**	**< 0.0001***
Prochlorperazine or metoclopramide with parkinsonism	-	1/3	-
PPI for peptic ulcer disease at full therapeutic dose for >8 weeks	85/96	38/115	< 0.0001*
Respiratory System	**-**	**1/3 (33.3%)**	**-**
Theophylline as monotherapy for COPD	-	1/1	-
Nebulised ipratropium with glaucoma	-	0/2	-
Musculoskeletal System	**15/20 (75%)**	**5/13 (38.5%)**	**0.0358***
NSAID with history of peptic ulcer disease or gastrointestinal bleeding unless with concurrent H_2 receptor antagonist, misoprostol or PPI	2/2	-	-
NSAID with moderate-severe hypertension	4/6	3/5	0.819
NSAID with heart failure	1/1	0/1	0.1573
Long-term (> 3 months) use of NSAIDs for symptom relief in mild osteoarthritis	6/9	1/3	0.3105
Warfarin and NSAID together	-	1/4	-
NSAIDs with chronic renal failure	2/2	-	-
Urogenital System	**9/12 (75%)**	**3/7 (42.9%)**	**0.1612**
Bladder anti-muscarinic drugs with dementia	4/7	1/2	0.8577
Anti-muscarinic drugs with glaucoma	1/1	-	-
Anti-muscarinic drugs with chronic constipation	3/3	2/5	0.0897
Alpha-blockers in males with frequent incontinence (≥ 1 episode daily)	1/1	-	-
Endocrine System	**-**	**0/1 (0%)**	**-**
Beta-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes	-	0/1	-
Drugs that adversely affect those prone to falls	**30/46 (65.2%)**	**12/36 (33.3%)**	**0.0042***
Benzodiazepines	19/27	10/26	0.0196*
Neuroleptic drugs	3/5	1/4	0.2937
1st generation antihistamines	2/2	0/2	0.0455*
Vasodilator drugs in those with persistent postural hypotension	1/1	-	-
Long-term opiates	5/11	1/4	0.4745

Analgesic drugs	**16/18 (88.9%)**	**7/9 (77.8%)**	**0.4436**
Regular opiates for >2 weeks in those with constipation without concurrent laxatives	12/14	7/9	0.6241
Use of long-term powerful opiates as first line therapy for mild-moderate pain	2/2	-	-
Long-term opiates in those with dementia unless indicated for palliative care or moderate-severe chronic pain syndrome	2/2	-	-
Duplicate drug class prescriptions	**23/28 (82.1%)**	**4/9 (44.4%)**	**0.0267***
Total	**237/292 (81.2%)**	**100/255 (39.2%)**	**< 0.0001***

COPD: Chronic Obstructive Pulmonary Disease. SSRI: Selective Serotonin Reuptake Inhibitor. PPI: Proton Pump Inhibitor.
NSAID: Non-steroidal anti-inflammatory drug. †*p*-value calculated using chi-squared test. * Statistically significant difference observed ($p < 0.05$).

Table 2: Prescriber Implementation Rates for START Recommendations: Physician versus Pharmacist

START criteria	Physician	Pharmacist	*p*-value
Cardiovascular System	**29/37 (78.4%)**	**4/15 (26.7%)**	**0.0005***
Warfarin with chronic atrial fibrillation	15/18	-	-
Aspirin with chronic atrial fibrillation where warfarin is contraindicated	2/3	0/1	0.2482
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm	0/2	2/5	0.2899
Antihypertensive therapy where systolic blood pressure consistently >160 mmHg	1/1	-	-
Statin therapy with history of coronary, cerebral, or peripheral artery disease without contraindication	8/9	1/3	0.0543
ACE-inhibitor with chronic heart failure	3/4	1/4	0.1573
ACE-inhibitor following acute myocardial infarction.	-	0/1	-
Beta-blocker with chronic stable angina	-	0/1	-
Gastrointestinal System	**1/1 (100%)**	**-**	**-**
Proton Pump Inhibitor with severe gastro-oesophageal acid reflux disease or peptic stricture requiring dilatation	1/1	-	-
Musculoskeletal System	**97/109 (89%)**	**6/19 (31.6%)**	**< 0.0001***
Bisphosphonates in patients taking maintenance oral corticosteroid therapy	14/18	1/10	0.0006*
Calcium and vitamin D supplementation in patients with known osteoporosis, fragility fracture or dorsal kyphosis	83/91	5/9	0.0017*
Endocrine System	**12/12 (100%)**	**3/10 (30%)**	**0.0004***
Metformin with type 2 diabetes mellitus +/- metabolic syndrome	1/1	-	-
ACE-inhibitor or angiotensin 2 receptor blocker in patients with diabetes and nephropathy	7/7	-	-
Antiplatelet therapy in those with diabetes mellitus and one or more major cardiovascular risk factors	2/2	1/1	‡
Statin therapy in patients with diabetes mellitus and one or more major cardiovascular risk factors	2/2	2/9	0.0386*
Total	**139/159 (87.4%)**	**13/44 (29.5%)**	**< 0.0001***

ACE: Angiotensin Converting Enzyme. †*p*-value calculated using chi-squared test. * Statistically significant difference observed ($p < 0.05$).
‡ *p*-value cannot be calculated.