An Interprofessional Student-Run Medication Review Program: The Clinical STOPP/START-Based Outcomes of a Controlled Clinical Trial in a Geriatric Outpatient Clinic

Rowan Sultan^{1,2,*,†}, Tessa O. van den Beukel^{1,2,†}, Michael O. Reumerman^{1,2}, Hester E. M. Daelmans³, Hans Springer⁴, Els Grijmans⁴, Majon Muller⁵, Milan C. Richir^{1,2}, Michiel A. van Agtmael^{1,2,†} and Jelle Tichelaar^{1,2,†}

As the population ages, more people will have comorbid disorders and polypharmacy. Medication should be reviewed regularly in order to avoid adverse drug reactions and medication-related hospital visits, but this is often not done. As part of our student-run clinic project, we investigated whether an interprofessional student-run medication review program (ISP) added to standard care at a geriatric outpatient clinic leads to better prescribing. In this controlled clinical trial, patients visiting a memory outpatient clinic were allocated to standard care (control group) or standard care plus the ISP team (intervention group). The medications of all patients were reviewed by a review panel ("gold standard"), resident, and in the intervention arm also by an ISP team consisting of a group of students from the medicine and pharmacy faculties and students from the higher education school of nursing for advanced nursing practice. For both groups, the number of STOPP/START-based medication changes mentioned in general practitioner (GP) correspondence and the implementation of these changes about 6 weeks after the outpatient visit were investigated. The data of 216 patients were analyzed (control group = 100, intervention group = 116). More recommendations for STOPP/START-based medication changes in the intervention group than in the control group (43% vs. 24%, P = < 0.001). After 6 weeks, a significantly higher proportion of these changes were implemented in the intervention group (19% vs. 9%, P = 0.001). The ISP team, in addition to standard care, is an effective intervention for optimizing pharmacotherapy and medication safety in a geriatric outpatient clinic.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The population is aging with, as a result, increasingly more patients with comorbidity and polypharmacy. Although guidelines advise that healthcare professionals should regularly review medication lists in order to reduce adverse drug reactions and medication-related hospital admissions, this is rarely done. Student-run clinics can improve prescribing and prescribing awareness.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is the addition of an interprofessional student-run medication review program team to standard care associated with more recommendations regarding medication changes?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The addition of an interprofessional student-run medication review team to standard care in an outpatient clinic led to an increased number of relevant medication-related recommendations. A student-run medication review team can make important suggestions about medications that need to be started or, perhaps more importantly, that need to be withdrawn.

HOW MIGHT THIS CHANGE CLINICAL PHARMA-COLOGY OR TRANSLATIONAL SCIENCE?

✓ Interprofessional student-run medication review teams are effective and low-cost interventions that could optimize medication safety in a clinical and outpatient setting.

¹Department of Internal Medicine section Pharmacotherapy, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; ²Research and Expertise Center in Pharmacotherapy Education (RECIPE), Amsterdam, The Netherlands; ³Skills Training Department, Faculty of Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Amsterdam, The Netherlands; ⁴Hogeschool Inholland, Amsterdam, The Netherlands; ⁵Department of Internal Medicine section Geriatric Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ⁴Hogeschool Inholland, Amsterdam, The Netherlands; ⁵Department of Internal Medicine section Geriatric Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands. *Correspondence: Rowan Sultan (*r.sultan@amsterdamumc.nl*)

[†]Contributed equally as first authors.

[†]Contributed equally as last authors.

Received June 25, 2021; accepted October 24, 2021. doi:10.1002/cpt.2475

Population aging means that increasingly more patients will have comorbidity and receive polypharmacy.¹ Polypharmacy increases the likelihood of adverse drug reactions (ADRs) and medicationrelated hospital visits. This is particularly true for geriatric patients because of age-related changes in drug pharmacokinetics and pharmacodynamics, and functional decline^{2,3}

Although guidelines advise that healthcare professionals should regularly review medication lists in order to reduce ADRs and medication-related hospital admissions,^{4–7} this is rarely done in practice⁸ for various reasons. Physicians may lack the necessary knowledge and skills in pharmacotherapy,^{9–11} because they did not receive appropriate general pharmacotherapy and geriatric pharmacotherapy education during their training.^{9,10,12,13} Moreover, there may not be enough time to optimize medications because the often too short consultation time is mainly spent on making a problem list, extracting the right diagnoses, and drawing up an appropriate treatment plan. This is apparent when reviewing the medications of elderly patients at an outpatient clinic or at the general practitioner's (GP) office.^{14,15}

Improvement of medical students' knowledge and skills in pharmacotherapy and greater awareness of potential medication problems on the part of physicians would improve medication safety.^{12,16} We have previously shown that student-run clinics can improve prescribing and prescribing awareness.¹⁷⁻²³ Student-run clinics offer students early prescribing experience with real responsibility for patient care and support physicians in their prescribing duties.^{24,25} Moreover, introducing a student-run clinic in a geriatric outpatient clinic, where most patients are on polypharmacy and vulnerable for ADRs, could optimize clinical outcomes because more attention can be paid to and time spent on the patient interview and the medication review. The aim of this study was to investigate whether the addition of an interprofessional studentrun medication review program (ISP) team to standard care at a geriatric outpatient clinic is associated with more recommendations to change medications in GP correspondence and more changes made in medication lists about 6 weeks after the outpatient assessment.

METHODS

Clinical setting

This controlled clinical trial was performed at a geriatric memory outpatient clinic in a tertiary academic hospital. The memory outpatient clinic is for patients aged 70 years who are suspected to have cognitive function decline.²⁶ Patients are referred by their GP, a medical specialist, or as second opinion from another hospital. During 1 day at the memory outpatient clinic, 4 patients can be planned for an outpatient clinic visit. These patients were assigned to a timeslot by a medical secretary, who was not involved in the study, without taking the suitability for the ISP into account. At the first visit, the patient is seen by a resident in internal medicine, psychiatry, or hospital medicine, under the supervision of an internist-geriatrician or geriatrician. The resident performs an anamnesis, which includes a medication analysis, and a physical examination. A nursing consultant of geriatric medicine performs additional physical and cognitive screening tests and a medical care interview with a relative or caregiver. A psychologist performs a neuropsychological examination, and general blood tests and neuroimaging are performed. The healthcare professionals' findings are discussed during a multidisciplinary meeting, 6 days after the assessment. Approximately 1 week after the multidisciplinary meeting, the patient and relative/caregiver have a second appointment to discuss the results. Then a letter is sent to the referring specialist and/or the GP explaining the findings and giving recommendations to change medication. The letter indicates who will be responsible for making these changes (the resident or the GP; Figure 1).

Interprofessional student-run medication review program

In 2017, we introduced a student-run clinic at the memory outpatient clinic, called the ISP, which is part of the community service learning program "A Broader Mind for students."²⁷ The ISP is coordinated by (non-paid) senior healthcare students and supervised by a physicianclinical pharmacologist. This program is part of the students' regular curriculum, and takes place during second-year courses and internships. Each week, a two-member team of students from different backgrounds (i.e., bachelor and master medical students, pharmacy students, physician assistant students, or advanced nursing practice students) evaluates the medication of two of the four patients attending the memory clinic.

The students have access to the Prescribing Optimization Method (POM)²⁸ and the second version of the STOPP/START criteria.²⁹ The POM was initially developed for GPs to assist them in optimizing polypharmacy in the elderly.²⁸ The STOPP/START criteria were developed to optimize the pharmacotherapy of older people and have been translated and adapted to the situation in the Netherlands.^{29,30} The students perform a 4-step ISP program, consisting of a: (i) 30-minute consultation with the patient and relative/caregiver regarding the medication history and medication list; (ii) structured medication review, using the POM and STOPP/START criteria; (iii) discussion of review findings with a clinical pharmacologist; and (iv) presentation of medication recommendations at the multidisciplinary meeting at the memory clinic and documentation of the findings in the electronic patient record.



Figure 1 Different steps at memory outpatient clinic for patients that receive standard care and patients that receive standard care plus the ISP intervention. ISP, interprofessional student-run medication review program. [Colour figure can be viewed at wileyonlinelibrary.com]

Study design

Patient inclusion for this study started October 30, 2018. The medical secretary (not involved in the study) assigned each patient to 1 of the 4 available timeslots with a 1:1 allocation without taking the suitability for the ISP into account. Initially, ISP was allocated to the patients in the third and fourth timeslots. To minimize possible bias, in the second half of the study, the ISP was allocated to the first and second timeslots. This formed two patient groups: standard care (control group) and standard care plus the ISP team (intervention group). The end of the study was set the day after 100 patients were included in both groups, based on the power calculation. Patients were eligible for study inclusion if they gave written informed consent before inclusion. Patients who were scheduled for a neuropsychological examination without first having a consultation were excluded from this study. Neither the patients nor the healthcare professionals nor the ISP team were blinded for allocation.

Medication review panel

The medication lists (i.e., the medication list entered by the resident into the electronic patient record during the outpatient assessment) of the included patients were reviewed by a review panel blind to group allocation. This review panel, whose function was to set the "gold standard," was not part of the standard care at this outpatient clinic and consisted of a clinical pharmacologist and a resident internal-geriatric medicine/clinical pharmacologist in training. They independently scored the number of potentially inappropriate medications and POMs according to the second version of the START/STOPP criteria.³⁰ Findings were discussed until consensus was reached. Ambiguities that came up during consensus meetings regarding the medical history were clarified by the senior healthcare student, using data from the electronic patient record (except from data noted by the ISP team).

Study outcomes

In order to determine the quality of prescribing about 6 weeks after the outpatient assessment, we determined the number of STOPP/START items (total, STOPP, and START) identified by the review panel that (i) had been identified by the resident at baseline, (ii) had been identified by the ISP at baseline, (iii) had been mentioned as treatment recommendations in the GP correspondence, and (iv) had been implemented, as evidenced by the medication overview provided by the community pharmacist 6 weeks after the outpatient assessment. We established whether the resident planned to make the STOPP/START-based medication changes or whether he/she passed this task on to the GP. We then compared the medication lists, obtained from the community pharmacist, of patients on the day of the outpatient assessment and 6 weeks later, to determine whether the medication changes had been made. If the community pharmacist did not send a patient's medication lists, even after a follow-up telephone call, the data of this patient were excluded from the analysis.

Statistical analyses

For the primary end point of this study, we estimated that at least 35 patients in each group would provide the study with 80% power to detect a clinically important difference, the identification of an extra 0.5 STOPP/START item per patient. Because of potential dropout, refusal to give informed consent, and other secondary outcomes, we estimated that 100 patients in each group would suffice. Baseline statistics are presented as means \pm SD or in case of a skewed distribution as median (interquartile range) for the two groups of patients. Differences between groups were analyzed with one-way analysis of variance or Mann-Whitney *U* test for continuous variables and chi-squared tests for categorical variables. Statistical significance was set at $P \leq 0.05$. Analyses were carried out with SPSS version 22.0 for Windows statistical software.



Figure 2 Flowchart of in- and excluded patients in the study, between October 30, 2018 and March 10, 2020. ISP, interprofessional studentrun medication review program.

Ethical considerations

The institutional review board concluded that the study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO, reference: 17.148). All patients signed an informed consent indicating their agreement to participate in the study, to allow the researchers to use their anonymized patient data, and to allow the researchers to contact the patient and their local pharmacy for follow-up. The study protocol was also approved by the ethics review board of the Netherlands Association for Medical Education (NVMO, ID:2019.2.1).

RESULTS

During the period October 30, 2018, to March 10, 2020, 216 patients were included (116 in the control group and 100 in the intervention group). Three patients (2 in the control group) were excluded because they did not provide informed consent (**Figure 2**). The baseline demographic, clinical, and medication characteristics of patients in the two groups were comparable, except for a higher use of nasal sprays in the control group (14.7% control group vs. 10.0% intervention group, P = 0.037). Patients were ~ 79 years of age, had a comorbidity index of 5, and used a median of 5 medications; about 56% of the patients were diagnosed with dementia during the outpatient clinic visit (**Table 1**).

STOPP/START items identified

Total items. At baseline, the review panel identified 251 STOPP/ START items (100%) in the control group (mean 2.2) and 206 items (100%) in the intervention group (mean 2.1). Of these items, the resident identified 17 (7%) in the control group and 14 (7%) in the intervention group; the ISP identified 128 STOPP/START items (62%) items in the intervention group. In total, 61 items (24%) in the control group and 89 items (43%) in the intervention group (P = < 0.001) were mentioned as recommended medication changes in the GP correspondence. About 6 weeks later, medication changes based on 22 STOPP/START items (9%) in the control group and 39 (19%) in the intervention group had been implemented (P = 0.001; **Table 2**).

STOPP and START items. At baseline, the review panel identified 166 STOPP items (100%) in the control group and 133 (100%) in the intervention group. The resident identified 16 STOPP items (10%) in the control group and 11 (8%) in the intervention group (P = 0.682); the ISP team identified 82 STOPP items (62%). In total, 31 STOPP-based medication changes (19%) in the control group and 54 STOPP-based changes (41%) in the intervention group (P = < 0.001) were mentioned in the GP correspondence. These STOPP-based changes included advice, such as stopping benzodiazepines and antipsychotics. After 6 weeks, more STOPP-based medication changes (n = 12, 17% vs. n = 13, 8%, respectively, P = 0.020), as had more START-based medication changes (n = 17, 23%, vs. n = 9, 11%, P = 0.032; **Table 2**).

Implementation of STOPP/START recommendations

Total items. The resident planned to implement 35 STOPP/ START-based medication changes (57%) in the control group and 33 (37%) in the intervention group (P = 0.014), assigning 26 (43%) medication changes in the control group and 56 (63%) medication changes in the intervention group to the GPs (P = 0.014). Six weeks later, the resident had made 22 medication changes in the control group and 20 in the intervention group (P = 0.849), and GPs had made 0 medication changes in the control group and 19 in the intervention group (P = 0.001; **Table 3**).

STOPP and START items. The resident delegated 13 (42%) STOPPbased medication changes in the control group and 39 (72%) in the intervention group (P = 0.006) to the GPs. In both groups, the resident planned to implement ~ 50% of the START-based medication changes themselves. Six weeks after the outpatient assessment, there was no significant difference between the STOPP- and START-based medication changes made by the resident (P = 0.458 and P = 0.625, respectively). There was a significant difference in the number of medication changes made by the GPs—0 STOPP-based changes in the control group and 13 (33%) in the intervention group (P = 0.023), and 0 START-based changes in the control group and 6 (35%) in the intervention group (P = 0.024; **Table 3**).

DISCUSSION

This controlled clinical trial showed that the addition of an ISP team to standard care increased the medication advice in the GP correspondence and the implementation of STOPP/START-based medication changes, as evidenced by changes in the medication lists of geriatric patients 6 weeks after an outpatient assessment.

To our knowledge, this is the first study to evaluate the clinical STOPP/START-based outcomes of a (interprofessional) student-run medication review team in an outpatient clinic. In our pilot study, we found that students had a valuable input in optimizing the medication lists of elderly patients,¹⁹ but we did not evaluate the clinical STOPP/START-based outcomes of this intervention compared with standard care. The results of our current study are in line with those of other studies showing positive effects of student-run clinics on general healthcare outcomes.^{31–34} However, in contrast to our study, most studies compared healthcare provided by students to a situation without available healthcare, which may have led to overly positive outcomes.³¹ Moreover, to our knowledge no (interprofessional) student-run intervention studies have evaluated clinical outcomes in terms of optimizing medication lists to improve medication safety.

In both groups, only 7% of the potentially problematic medication issues identified by the review panel were recorded in the electronic patient record during the outpatient assessment. After this was discussed in a multidisciplinary meeting with the supervisors and other residents, there was an increased identification of STOPP/START items in both groups. In the group receiving standard care, 24% of the STOPP/START-based medication recommendations were mentioned in the GP correspondence. The addition of the ISP team to standard care significantly increased the number of STOPP/START recommendations to 43%. The

Table 1 Baseline characteristics in patients who received standard care and patients who received the ISP in addition to standard care

		Standard care (<i>n</i> = 116)	Standard care + ISP (n = 100)	P value
Demographic characteristics				
Age, years, mean (SD)		79.57 (5.516)	78.81 (5.181)	0.301
Sex, male (%)		63 (54.3)	51 (51.0)	0.627
Living arrangements			. ,	
Alone (%)		42 (36.2)	42 (42.0)	0.384
With partner or family (%)		63 (54.3)	51 (51.0)	0.627
Sheltered housing (%)		9 (7.8)	3 (3.0)	0.128
Residential care (%)		2 (1.7)	4 (4.0)	0.310
Clinical characteristics				
Charlson comorbidity index, median (IQR)		5.00 (4-6)	5.00 (4-6)	0.519
Orthostatic hypotension, yes (%)		26 (22.4)	20 (20.0)	0.666
Falling in the previous year, yes (%)		21 (18.1)	12 (12.0)	0.214
Cognitive diagnosis		19 (16.4)	20 (20.0)	0.490
No cognitive disorder (%)		30 (25.9)	26 (26.0)	0.982
Mild cognitive impairment (%)		67 (57.8)	54 (54.0)	0.579
Dementia (%)		68.69 (15.1)	69.74 (14.9)	0.608
eGFR, mL/min/1.73 m ² (mean, SD)				
Medication				
Total number of medications		630	551	0.878
Median (IQR)		5.00 (3-8)	5.00 (3-7.75)	0.878
n = 0 (%)		5 (4.3)	6 (6.0)	0.573
n = 1 - 4 (%)		46 (39.7)	38 (38.0)	0.804
n = 5-9 (%)		50 (43.1)	42 (42.0)	0.870
<i>n</i> = ≥ 10 (%)		15 (12.9)	14 (14.0)	0.818
ATC code	ATC code description			
A (%)	Alimentary tract and metabolism	81 (69.8)	73 (73.0)	0.607
A02 (%)	Drugs for acid related disorders	41 (35.3)	45 (45.0)	0.148
A10 (%)	Drugs used in diabetes	16 (13.8)	13 (13.0)	0.865
B (%)	Blood and blood forming organs	56 (48.3)	49 (49.0)	0.915
B01 (%)	Antithrombotic agents	55 (47.4)	49 (49.0)	0.816
C (%)	Cardiovascular system	71 (61.2)	67 (67.0)	0.377
C03 (%)	Diuretics	17 (14.7)	21 (21.0)	0.222
C07 (%)	Beta blocking agents	24 (20.7)	27 (27.0)	0.276
C08 (%)	Calcium channel blockers	19 (16.4)	22 (22.0)	0.294
C09 (%)	Agents acting on renin-angiotensin system	39 (33.6)	40 (40.0)	0.332
C10 (%)	Lipid modifying agents	52 (44.8)	45 (45.0)	0.980
G (%)	Genito-urinary system and sex hormones	19 (16.4)	12 (12.0)	0.360
GO4 (%)	Urologicals	19 (16.4)	12 (12.0)	0.360
N (%)	Nervous system	41 (35.5)	35 (35.0)	0.958
N02 (%)	Analgesics	17 (14.7)	16 (16.0)	0.784
N03 (%)	Antiepileptics	3 (2.6)	4 (4.0)	0.558
N05 (%)	Psycholeptics	21 (18.1)	20 (20.0)	0.723
N06 (%)	Psychoanaleptics	17 (14.7)	17 (17.0)	0.637
R (%)	Respiratory system	28 (24.1)	13 (13.0)	0.037
R03 (%)	Drugs for obstructive airway disease	17 (14.7)	10 (10.0)	0.302

ATC, Anatomic Therapeutic Chemical; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ISP, interprofessional student-run medication review program.

Standard care (n = 116)Standard care + ISP (n = 100) P value **Total items** Total items Total START (%) (%) STOPP (%) STOPP (%) START (%) items STOPP START (%) Review panel 251 (100) 166 (100) 85 (100) 206 (100) 133 (100) 73 (100) 0.608 0.603 0.906 Resident 0.992 0.682 0.336 17(7)16 (01) 1(1)14(7)11 (8) 3 (4) ISP team 128 (62) 82 (62) 46 (63) _ GP correspondence 61 (24) 31 (19) 30 (35) 89 (43) 54 (41) 35 (48) < 0.001 < 0.001 0.107 Medication list 22 (9) 13 (8) 9 (11) 39 (19) 22 (17) 17 (23) 0.001 0.020 0.032 6 weeks after the

Table 2 Number of STOPP/START items identified by the review panel, residents, and the ISP team during the outpatient assessment that were mentioned in the GP correspondence and changed in the medication list of the community pharmacist 6 weeks after the assessment

assessment

GP, general practitioner; ISP, interprofessional student-run medication review program.

ISP team made approximately nine times more medication recommendations (14 vs. 128) than the residents. These data support the notion that consulting time is mainly focused on diagnosis and drawing up a treatment plan instead of optimizing medication,¹⁵ thereby underlining the important role an ISP team can have in reviewing patient medication.

Most of the STOPP-based medication recommendations (72%) mentioned in the GP correspondence were delegated to GPs to implement, whereas 57% of the STOPP/START-based medication recommendations in the control group were implemented by residents. This difference might be due to the difficult nature of the STOPP-based recommendations advised by the ISP team, such as stopping benzodiazepines or antipsychotics. The process of deprescribing is gaining attention in clinical practice, and there is evidence that deprescribing can reduce the risk of medication-related harm.³⁵ However, deprescribing is complicated—it requires interdisciplinary collaboration and is time-consuming, so that many healthcare professionals tend to avoid deprescribing.³⁶ Our findings suggest that an ISP team could have an important role in deprescribing. Moreover, we found that of all the medication recommendations made to GPs, more made for the intervention

group than for the control group were implemented, suggesting that GPs considered these recommendations relevant.

Our study had some strengths and limitations. The main strength is that all parties benefitted-students gained the opportunity to learn in an authentic setting, while improving clinical STOPP/ START-based outcomes, residents had more time to focus on aspects other than medication review, their awareness of the importance of reviewing medication increased, and patients received an optimized medication list. Another strength lies in the controlled clinical trial design, where we evaluated the value of the ISP team in addition to standard care compared with standard care only, describing each step of the process. This made it possible to follow how treatment recommendations were handled. The third strength is the large number of patients (n = 216) included, the lack of dropout, and the availability of medication lists for the 6-week follow-up. Last, the implementation and running costs were low. Although most pharmacist- and physician-led interventions are not cost-effective,^{3/} the ISP team is run by non-paid healthcare students who only need to be supervised by a physician-clinical pharmacologist for 10 minutes.

There were several potential limitations. First, the team of healthcare professionals at the multidisciplinary meeting significantly

	Standard care (n = 116)			Standard care + ISP (n = 100)		P value			
	Total items (%)	STOPP (%)	START (%)	Total items (%)	STOPP (%)	START (%)	Total items	STOPP	START
In GP correspondence	61 (100)	31 (100)	30 (100)	89 (100)	54 (100)	35 (100)	< 0.001	< 0.001	0.146
To be imple- mented by the resident	35 (57)	18 (58)	17 (57)	33 (37)	15 (28)	18 (51)	0.014	0.006	0.673
Implemented by the resident	22 (63)	13 (72)	9 (53)	20 (61)	9 (60)	11 (61)	0.849	0.458	0.625
To be imple- mented by the GP	26 (43)	13 (42)	13 (43)	56 (63)	39 (72)	17 (49)	0.014	0.006	0.673
Implemented by the GP	0 (0)	0 (0)	0 (0)	19 (34)	13 (33)	6 (35)	0.001	0.023	0.024

Table 3 Number of STOPP/START items mentioned in the GP correspondence, stratified by the healthcare professional who would implement the relevant medication change, and whether the change was implemented 6 weeks after the outpatient assessment

GP, general practitioner.

increased the number of medication recommendations additional to those made by the residents. However, the medication of all patients was discussed in these meetings and even though more STOPP/START-based medication recommendations were added in the multidisciplinary meeting, there were still significant differences in the recommendations made in the GP correspondence between the control and intervention groups. Moreover, these discussions may have raised a more general awareness of medication safety and thereby increased the number of medication recommendations. If so, the results of our study underestimate the real effect of adding an ISP team to standard care. Second, although the memory outpatient clinic is primarily focused on memory-related problems and not on the optimization of medication lists, many memoryrelated problems are correlated with medication use. As elderly patients are more susceptible to medication-related ADRs,^{2,3} they would benefit from a thorough medication review, such as that provided by the ISP team. Last, we do not know why GPs chose not to implement all the medication recommendations mentioned in the GP correspondence, but they did implement a greater proportion of the recommendations made for patients in the intervention group compared with those for patients in the control group.

In conclusion, the ISP intervention has already proven effective in providing students with learning opportunities and responsibility for real patients while working in an interprofessional setting.¹⁹ In this study, we demonstrated that the addition of an interprofessional student-run medication review team to standard care in an outpatient clinic led not only to an increased number of relevant medicationrelated recommendations noted in GP correspondence but also to optimization of patient medication lists 6 weeks after the outpatient assessment. A student-run medication review team can make important suggestions about medications that need to be started or, perhaps more importantly, that need to be withdrawn. Unlike most studies on interprofessional education (IPE), we demonstrated the importance of IPE for clinical STOPP/START-based outcomes, which is part of the World Health Organization's IPE definition.^{38,39} Because this intervention study was successful, we now review the medication of all patients attending the memory clinic, and other healthcare professionals are enquiring about the possibility of implementing a student-run medication review team in their outpatient clinics.

Further study is needed to examine whether there is further improvement of medication lists in the long term, and whether medication optimization leads to better health-related quality of life, patient medication satisfaction, and clinical results, such as fewer adverse drug events and associated hospitalizations. The learning benefits of this approach for future healthcare professionals should also be investigated.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. R.S., T.O.B., M.O.R., M.C.R., M.A.A., and J.T. designed the research. R.S., T.O.B., M.O.R., and J.T. performed the research. R.S., T.O.B., and M.O.R. analyzed the data.

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