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ORIGINAL RESEARCH

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An inter-professional student-run medication review programme. Reducing adverse drug reactions in a memory outpatient clinic: a controlled clinical trial

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ABSTRACT

Background: We investigated if the addition of an inter-professional student-led medication review team (ISP-team) to standard care can increase the number of detected ADRs and reduce the number of ADRs 3 months after an outpatient visit.

Research design and methods: In this controlled clinical trial, patients were allocated to standard care (control group) or standard care plus the ISP team (intervention group). The ISP team consisted of medical and pharmacy students and student nurse practitioners. The team performed a structured medication review and adjusted medication to reduce the number of ADRs. Three months after the outpatient visit, a clinical pharmacologist who was blinded for allocation performed a follow-up telephone interview to determine whether patients experienced ADRs.

Results: During the outpatient clinic visit, significantly more ($p < 0.001$) ADRs were detected in the intervention group (n = 48) than in the control group (n = 10). In both groups, 60–63% of all detected ADRs were managed. Three months after the outpatient visit, significantly fewer (predominantly mild and moderately severe) ADRs related to benzodiazepine derivatives and antihypertensive causing dizziness were detected in the patients of the intervention group.

Conclusions: An ISP team in addition to standard care increases the detection and management of ADRs in elderly patients resulting in fewer mild and moderately severe ADRs.

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Medication safety; optimizing medication safety; elderly care; pharmacotherapy; pharmacovigilance

1. Introduction

With the average age of the population rising, the number of patients with multimorbidity and polypharmacy has increased over the last decades [1]. Many comorbidities, such as cognitive disorders, reduced glomerular filtration rate, and cardiovascular disease, as well as polypharmacy are risk factors for adverse drug reactions (ADRs) [2,3]. Regardless of their severity, ADRs are a frequent cause of visits to the emergency department and hospital admission (10–15%) and can have a significant impact on health-related quality of life and have a high prevalence in outpatient care settings (up to 78%) [2,4].

Despite being common, ADRs, and especially mild and moderately severe ADRs, often go undetected and untreated [5,6]. Reasons for this ADR unawareness in healthcare professionals are time constraints in clinical practice combined with a lack of pharmacological knowledge of ADRs [7,8]. This is not surprising since under- and postgraduate curricula devote little curriculum time to general pharmacotherapy education and even less to geriatric pharmacotherapy education or medication reviews [9,10]. The lack of knowledge, in combination with the increasingly specialized goals of outpatient clinics, may explain why there appears to be too little attention paid to optimizing medication and detecting and treating ADRs. This is especially worrying with regard to elderly patients with cognitive decline, as these individuals may have difficulties remembering ADRs and talking about their health [11–13]. Despite taking longer to evaluate, elderly patients remain at greater risk of inappropriate prescribing and ADRs caused by cardiovascular drugs, analgesics, and antidiabetics [4].

This vulnerability of older patients prompted us to develop an intervention to teach future prescribers to optimize medication and to detect and treat ADRs in patients with cognitive decline. This educational intervention, the inter-professional student-led medication review team (ISP team), is run by an inter-professional team of healthcare students (medicine, pharmacy, and nurse practitioner) who review the medication of elderly patients at a memory outpatient clinic. The ISP team

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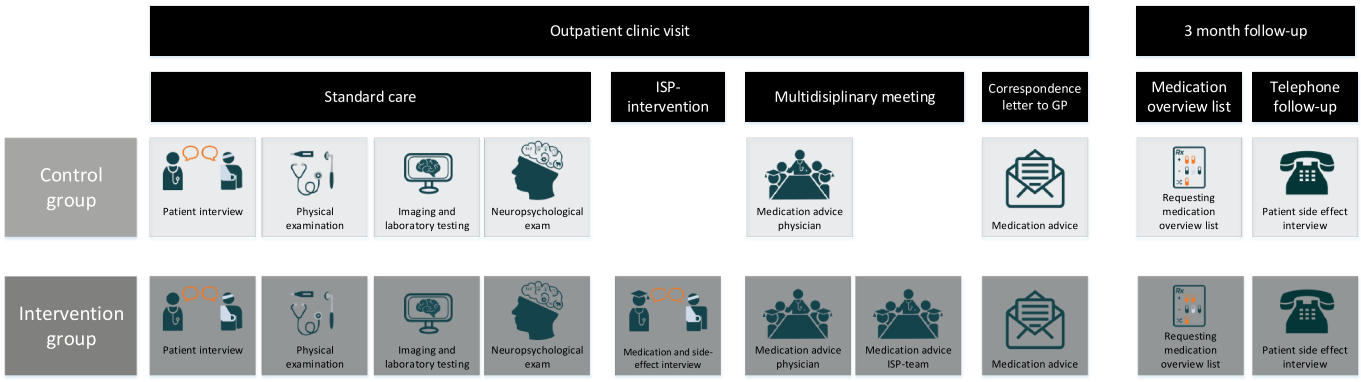

Figure 1. Inter-professional student-run medication review program procedure and follow-up.

has proven its worth in the diagnosis of ADRs and has a clinical value on top of standard care in optimizing the medication list of patients during an outpatient clinic [14,15]. We have not assessed the clinical value of the ISP team in terms of detecting, managing and reducing the number of ADRs when added to standard care. Therefore, our main objective in this study was to investigate whether the addition of the ISP team to standard care is associated with a reduction of ADRs 3 months after the outpatient visit. Secondary objectives in this study were to investigate if the addition of the ISP team to standard care is associated with the detection and management of more ADRs during the outpatient visit.

2. Methods

2.1. Setting and patients

This controlled clinical trial, with an allocation ratio of 1:1, was performed at a memory outpatient clinic in an academic hospital. The patient group consisted of older patients (most were aged 70 years or older) who were suspected of cognitive decline [16]. The memory outpatient clinic assesses four patients a week who are suspected of cognitive function decline.

At the memory clinic, four patients (and their caregivers) per week receive multiple, serial consultations by a resident (internal medicine, psychiatry, or hospital medicine), a supervisor (internist-geriatrician or geriatrician), a nursing consultant geriatric medicine, and a neuropsychologist. On the same day, all patients undergo additional laboratory testing (complete blood count, electrolytes, kidney function, liver panel, thyroid hormones, full cholesterol panel and vitamin D & B12) and an MRI scan (or CT scan) of the brain.

One week after the consultation, the findings are discussed in a multidisciplinary meeting. One week later, the patient and caregivers meet with resident (internal medicine, psychiatry, or hospital medicine) to discuss the results. A correspondence letter is sent to the referring physician, explaining the clinical findings and advice [15].

2.2. ISP procedure

The ISP is a collaboration between a Learner-Centered Student Run Clinic (LC-SRC) [17–20] and a memory outpatient clinic in an academic hospital. It is coordinated by a (non-paid) senior healthcare student and supervised by a clinical pharmacologist and the internist-geriatrician or geriatrician). Each week, a two-member team of bachelor and master medical students, pharmacy students, or student nurse practitioners evaluate the medication and side effects of two of the four patients during a 30-minute medication interview.

The ISP team is equipped with documentation regarding the Prescribing Optimalization Method (POM) [21], START-STOPP criteria [22], and medication trigger list [23,24]. The students performed a 4-step ISP program, consisting of: 1). Consultation (30 minutes) with the patient and relative/caregiver regarding the medication history, medication list, and ADRs; 2). Structured medication review; 3). Discussion of review findings with a clinical pharmacologist; 4). Presentation of their medication advice at the multidisciplinary meeting and documentation of the findings in the electronic healthcare record (Figure 1).

2.3. Study design

Patients who visited the outpatient clinic were allocated to the standard care group (control group) or standard care + ISP intervention group (intervention group) based on their time slot allocation by a medical secretary, who was not involved in the study. In the first half of the study, patients in the first and second timeslots were allocated to the control group, those in the third and fourth timeslots were allocated to the intervention group. To minimize possible bias, the ISP intervention switched to the first and second timeslot in the second half of the study. Patients were eligible for study inclusion if they gave written informed consent before inclusion and had a caregiver present at the outpatient clinic visit and follow-up patient interview. Patients who were scheduled for a neuropsychological

examination without first having a consultation were excluded from this study.

2.4. Outcome measures

A clinical pharmacologist, who was blinded for allocation, analyzed all ADRs reported in the electronic healthcare record by either the physicians or ISP team after the first consultation. ADRs were verified if they were 'possibly' related to the use of the medication (according to the WHO causality assessment scale and Naranjo algorithm [25,26] and scored on avoidability (by Hallas et al. [27]) and preventability (on the Schumock and Thornton scale [28]). All verified ADRs were categorized by severity (according to the Hartwig severity scale [29]) and all ADR details and advice to treat the ADR (stop drug, lower dose, other) were recorded.

2.4.1. Adverse drug reactions at follow-up

Patients were interviewed again about ADRs, 3 months after the correspondence letter was sent to the general practitioner. The interview was performed by telephone by a clinical pharmacologist who was blinded to the patient assignment. Patients who could not be reached after three attempts at weekly intervals or who did not have a caregiver present were classified as 'lost to follow-up.'

During the ADR interview, the previously detected ADRs, current medication list and medication changes since the patient visit were available for the clinical pharmacologist. Patients were first asked to report any new health problem or change in their condition since their outpatient visit. If they reported a health problem, they were asked to describe the severity of each new problem and indicate when it started in relation to the initiation of drug treatment, in order to classify the symptoms according to the WHO causality assessment scale and Naranjo algorithm. The nature, severity [29], avoidability (by Hallas et al. [27]) and preventability (on the Schumock and Thornton scale [28]) of the ADRs reported at first consultation were also reevaluated.

2.5. Ethical considerations

The institutional review board the academic hospital reviewed the protocol and concluded that the study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) (reference: 17.148). Because this study was part of a larger longitudinal cohort study, that was registered separately, this study was not registered. Patient signed multiple informed consent forms before being included (for the use of patient data at baseline, for the telephone interview at 3 months, and for access to their medication list at 3 month). Our protocol was also approved by the ethics review board of the Netherlands Association for Medical Education (NVMO) (ID:2019.2.1).

2.6. Data analysis

For the primary end point of this study, we estimated that at least 70 patients in each group would provide the study with 80% power to detect a clinically important difference, a difference of 0.25 identified side effects per patients at 3-month follow-up. Because of potential drop outs, refusal to give informed consent and other secondary outcomes, we estimated that including 100 patients in each group would suffice. Data were analyzed using SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA). Baseline characteristics are presented as medians (interquartile range, IQR), stratified by group. Differences in the baseline characteristics and between the number of ADRs in the control and intervention groups were assessed using Fisher-exact tests. Differences in total number of ADRs between the control and intervention group were assessed using Mann–Whitney U tests. Agreement in causality was calculated by dividing the number of ADRs with the same causality assessment by the total number of ADRs detected.

3. Results

From November 2018 to March 2020, 140 time slots were assigned to the standard care group (control group) and 140 to the standard care + ISP intervention (intervention group). Because of 61 unoccupied timeslots (control group n = 22 and intervention group n = 39) and unsigned informed consent forms for acquiring baseline information (n = 3), we included 216 patients at baseline. Because of unsigned consent forms for the 3-month follow-up (control group n = 36 and intervention group n = 27), patients who were lost to follow-up (n = 5), and patients who died (n = 6), 142 patients completed the follow-up (control group n = 76 and intervention group n = 66) (Figure 2).

3.1. Patients characteristics

The patient population consisted of 142 predominantly (94%) community dwelling elderly patients. They had a median comorbidity index of 5, used a median of 5 medications and 52% were diagnosed with dementia during the outpatient visit. At baseline, the two groups were comparable regarding their demographics, and clinical and medication characteristics, although the patients in the control group were significantly older (control group mean 79.5 years, intervention group mean 77.6 years; p = 0.026) and used more respiratory drugs (control group 32.9%, intervention group 15.2%; p = 0.014) than the patients in the intervention group (Table 1).

3.2. Adverse drug reactions at baseline

During the outpatient visits, 38 mild ADRs (level 1 & 2) and 20 moderately severe ADRs (level 3 & 4) were detected. More ADRs were detected in the intervention group (n = 48) than in the control group (n = 10; p < 0.001). Of the 48 ADRs detected in the intervention group, 4 were detected by the physician and were missed by the ISP-team, 5 were detected by the physician and the ISP-team separately and 44 ADRs were detected by the ISP-team and were missed by the physician. No significant differences were found between the total number of physician-detected ADRs in the control and intervention groups. Overall, 3 level 4 ADRs were detected in the

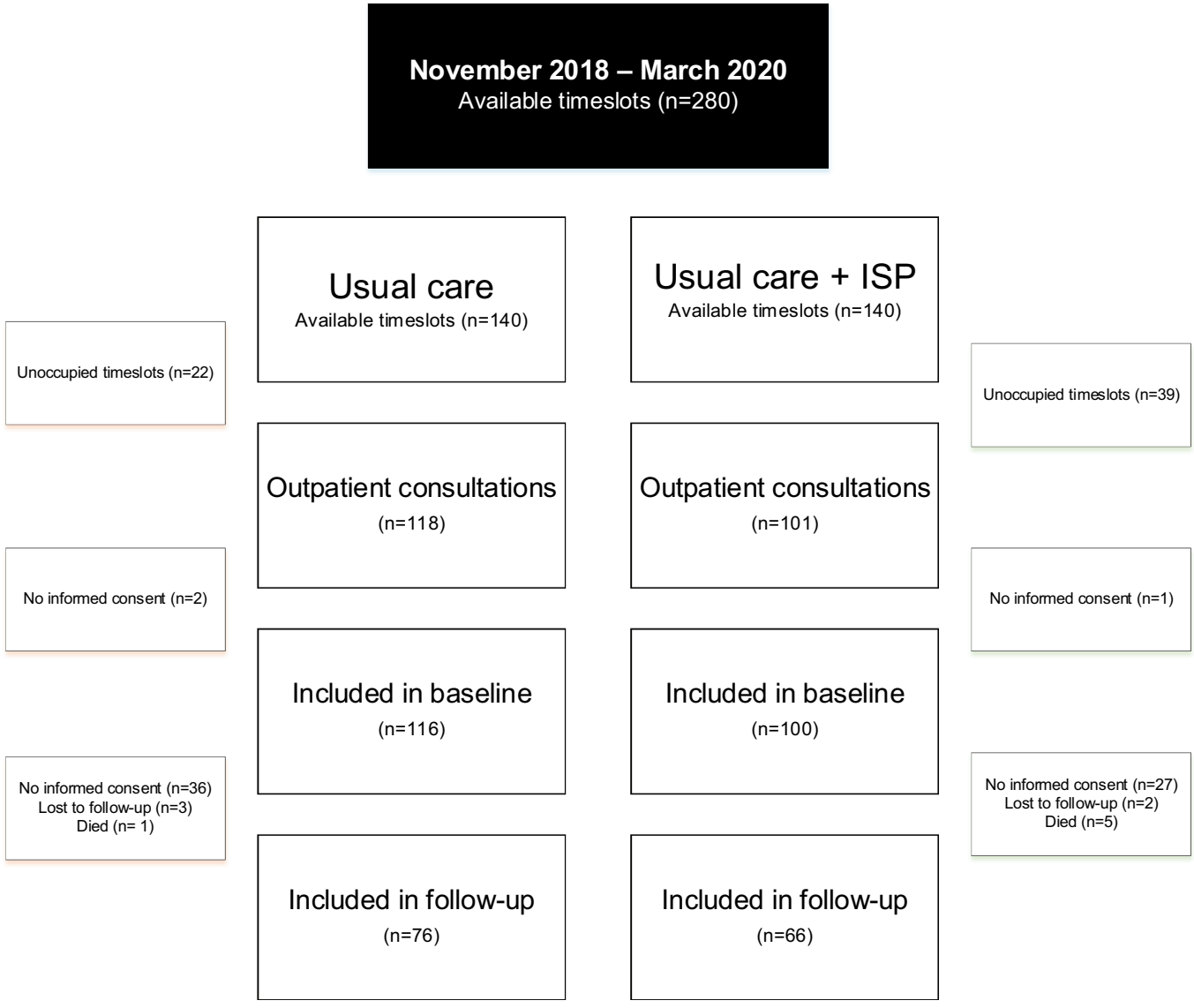

Figure 2. Flow diagram of the inclusion and exclusion of patients in this study.

control group and 4 in the intervention group ($p = 0.562$), whereas significantly more level 1–3 ADRs were detected in the intervention group than in the control group ($p < 0.001$, $P < 0.001$, and $p < 0.049$, respectively) (Table 2).

Causality assessment (WHO-UMC causality scale and Naranjo algorithm) revealed that 30–40% of the ADRs in the control group and 50–52% of the ADRs in intervention-group were at least probable related to the drug. Most ADRs were avoidable or preventable (67%–80%) (Table 3) and were caused by benzodiazepine derivatives (n = 13), antihypertensive drugs (n = 12), analgesics (n = 9), and urological drugs (n = 9). More ADRs caused by antihypertensives ($p = 0.002$), antidiabetics ($p = 0.004$), cholesterol-lowering drugs ($p = 0.004$), and antithrombotic agents ($p = 0.007$) were detected in the intervention group than in the control group (Table 4). The most frequently detected ADRs were dizziness (n = 29) and confusion (n = 14). Dizziness ($p < 0.001$), gastrointestinal disorders ($p = 0.002$), and musculoskeletal disorders ($p = 0.004$) were detected more often in the intervention group than in the control group (Table 5).

3.3. Medication interventions for ADRs

Thirty-six ADR interventions were suggested to manage the 58 ADRs (62% of ADRs received an intervention): 6 for ADRs in the control group (60% of ADRs detected) and 30 for ADRs in the intervention group (63% of ADRs detected) ($p = 0.981$). In both groups, most ADR interventions concerned drug discontinuation or lowering the dose. In the intervention group, 6 ADR changes concerned the time of drug administration and starting a drug to relieve the ADR. Although moderately severe ADRs (level 3–4) were more likely to be treated than were mild ADRs (level 1–2) (90% vs 47%), no differences were observed between the control and intervention groups (Table 2).

3.4. Adverse drug reactions at 3 months follow-up

At 3-month follow-up, less ADRs (n = 13) that require treatment (Hartwig severity level >1) were found in the

Table 1. Baseline characteristics.

		Control group (n = 76)	Intervention group (n = 66)	P value
Demographic characteristics				
Age (yrs), mean (SD)*		79.5 (5.1)	77.6 (4.8)	0.026
Sex, male (%)		41 (53.9)	35 (53.0)	0.913
Living arrangements				
Alone		24 (31.6)	30 (45.5)	0.089
With partner or family		47 (61.8)	33 (50.0)	0.156
Sheltered housing		5 (6.6)	2 (3.0)	0.330
Residential care		0 (0)	1 (1.5)	0.282
Clinical characteristics				
Charlson comorbidity index, median (IQR)*		5 (4–6)	5 (4–6)	0.926
Orthostatic hypotension, yes (%)		16 (21.1)	11 (16.7)	0.507
Falling in the previous year, yes (%)		15 (19.7)	8 (12.1)	0.219
Cognitive diagnosis				
No cognitive disorder		15 (19.7)	17 (25.8)	0.392
Mild cognitive impairment		22 (28.9)	14 (21.2)	0.291
Dementia		39 (51.3)	35 (53.0)	0.838
eGFR, mL/min/1.73 m^2 (mean, SD)*		69.4 (15.2)	72.5 (14.4)	0.219
Medication				
Total number of medications*		421	370	0.923
*median (IQR)**		5 (2.25–8)	5 (2–7.5)	0.923
n = 0 (%)		4 (5.3)	4 (6.1)	0.837
n = 1–4 (%)		31 (40.8)	25 (42.2)	0.723
n = 5–9 (%)		31 (40.8)	26 (39.4)	0.866
n = ≥10 (%)		10 (13.2)	11 (16.9)	0.557
Medication types				
ATC-code	ATC-description			
A	Alimentary tract and metabolism	53 (69.7)	47 (71.2)	0.848
A02	Drugs for acid related disorders	25 (32.9)	30 (45.5)	0.125
A10	Drugs used in diabetes	9 (11.8)	10 (15.2)	0.563
B	Blood and blood forming organs	36 (47.4)	33 (50.0)	0.754
B01	Antithrombotic agents	36 (47.4)	33 (50.0)	0.754
C	Cardiovascular system	43 (56.6)	43 (65.2)	0.297
C03	Diuretics	8 (10.5)	12 (18.2)	0.191
C07	Beta blocking agents	15 (19.7)	15 (22.7)	0.663
C08	Calcium channel blockers	10 (13.2)	13 (19.7)	0.291
C09	Agents acting on the renin-angiotensin system	25 (32.9)	23 (34.8)	0.806
C10	Lipid modifying agents	35 (46.1)	30 (45.5)	0.943
G	Genito-urinary system and sex hormones	13 (17.1)	8 (12.1)	0.404
G04	Urologicals	13 (17.1)	8 (12.1)	0.404
N	Nervous system	26 (34.2)	26 (39.4)	0.523
N02	Analgesics	11 (14.5)	11 (16.7)	0.719
N03	Antiepileptics	2 (2.6)	3 (4.5)	0.537
N05	Psycholeptics	12 (15.8)	14 (21.2)	0.405
N06	Psychoanaleptics	11 (14.5)	13 (19.7)	0.407
R	Respiratory system	25 (32.9)	10 (15.2)	0.014
R03	Drugs for obstructive airway diseases	16 (21.1)	10 (15.2)	0.364

Table 1: Baseline characteristics of patients who received standard care (control group) and patients who received the ISP intervention added to standard care (intervention group). Significance was calculated using Fisher exact test except * were calculated using Mann–Whitney U test.

intervention group compared to the ADRs detected at baseline (n = 32). The frequency of ADRs not requiring treatment (Hartwig severity level 1) did not change. Additionally, fewer ADRs were detected in the intervention group (n = 30) than in the control group (n = 52) (p = 0.006). This difference was accounted for by fewer level 2 and 3 ADRs in the intervention group than in the control group (p = 0.028 and p = 0.043 respectively); there was no difference in level 1 or level 4 ADRs between the two groups. (Table 2).

A high agreement rate between WHO-UMC causality scale and Naranjo algorithm was found (96%). Causality assessment found that 48% of the ADRs in the control group and 37–40% of the ADRs in intervention group were at least probable related to the drug. There was no difference in level of causality between the ADRs detected at baseline (%probable or higher: 47–50%) and the ADRs detected at 3-months follow-up (%probable or higher: 44–45%). Less ADRs were avoidable or preventable in the intervention group (40–47%) compared to the control group (71 – 77%) (Table 3).

Benzodiazepine derivatives (n = 19) and antihypertensive drugs (n = 17) were still the most frequent drug class causing ADRs at the 3-month follow-up. There were significantly (p = 0.043) more ADRs related to antihypertensive drugs in the control group than in the intervention group. Although not significantly different, we also detected at least twice as many ADRs related to antidiabetics (n = 9 vs n = 4) and lipid-modifying agents (n = 8 vs n = 3) and four times as many ADRs related to antithrombotic agents (n = 8 vs n = 2) in the intervention group than in the control group (Table 4).

At the 3-month follow-up, dizziness (n = 29) and confusion (n = 13) were still the most frequently detected ADRs. Dizziness was detected in fewer patients in the intervention

Table 2. Frequency of adverse drug reactions (ADRs) at baseline and 3-month follow-up.

	Control group (n = 76)	Intervention group (n = 66)			P-value
ADRs at baseline	Physician	Physician	ISP-team	Physician and ISP-team combined	
Patients with ≥1 ADRs (% of patients)	6 (7.9)	6 (9.1)	21 (31.8)	22 (33.3)	<0.001
Total number or ADRs*	10	9	44	48	<0.001
Severity					
Level 1 ADRs (% of patients)	1 (1.3)	0 (-)	16 (24.2)	16 (24.2)	<0.001
Level 2 ADRs (% of patients)	2 (2.6)	2 (3.0)	17 (25.8)	19 (28.8)	<0.001
Level 3 ADRs (% of patients)	4 (5.2)	3 (4.5)	7 (10.6)	9 (13.6)	0.049
Level 4 ADRs (% of patients)	3 (3.9)	4 (6.1)	4 (6.1)	4 (6.1)	0.562
ADR intervention					
Total number interventions (% of total ADRs)	6 (60)	6 (67)	28 (64)	30 (63)	0.981
Drug discontinued (% of total ADRs)	3 (30)	4 (67)	16 (36)	18 (38)	
Dose lowered (% of total ADRs)	3 (30)	2 (33)	6 (14)	6 (13)	
Other (% of total ADRs)	0 (-)	0 (-)	6 (14)	6 (13)	
Interventions classified to severity					
Level 1 (% of level 1 ADRs)	0 (-)	0 (-)	6 (38)	6 (38)	0.145
Level 2 (% of level 2 ADRs)	1 (50)	0 (-)	11 (65)	11 (58)	0.249
Level 3 (% of level 3 ADRs)	2 (50)	2 (67)	7 (100)	9 (100)	0.148
Level 4 (% of level 4 ADRs)	3 (100)	4 (100)	4 (100)	4 (100)	0.057
Total number of ADRs at 3 months					
Patients with ≥1 ADRs	25 (32.9)		16 (24.2)		0.256
Total number or ADRs *	52		30		0.006
Severity					
Level 1 ADRs (% of patients)	16 (21.1)		17 (25.8)		0.508
Level 2 ADRs (% of patients)	22 (28.9)		9 (13.6)		0.028
Level 3 ADRs (% of patients)	13 (17.1)		4 (6.1)		0.043
Level 4 ADRs (% of patients)	1 (1.3)		0 (-)		0.350

Table 2: Frequency of adverse drug reactions at baseline and 3-month follow-up in patients who received standard care (control group) and patients who received the ISP intervention added to standard care (intervention group). Significance was calculated using Fisher exact test except * were calculated using Mann–Whitney U test.

Table 3. Causality and avoidability assessment of the adverse drug reactions.

		Control group		Intervention group	
Features	Parameters	Baseline (n = 10)	3-months follow-up (n = 52)	Baseline (n = 48)	3-months follow-up (n = 30)
Causality (Naranjo algorithm)	Doubtful	-	-	-	-
	Possible	6 (60%)	27 (52%)	23 (48%)	18 (60%)
	Probable	4 (40%)	25 (48%)	24 (50%)	12 (40%)
	Definite	-	-	1 (2%)	-
Causality (WHO-UMC causality)	Unclassifiable/unclassified	-	-	-	-
	Unlikely	-	-	-	-
	Possible	7 (70%)	27 (52%)	24 (50%)	19 (63%)
	Probable	3 (30%)	25 (48%)	23 (48%)	11 (37%)
	Certain	-	-	1 (2%)	-
Avoidability (Hallas et al)	Unavoidable	3 (30%)	15 (29%)	16 (31%)	18 (60%)
	Possible avoidable	3 (30%)	21 (40%)	20 (42%)	8 (27%)
	Definitely avoidable	4 (40%)	16 (31%)	12 (25%)	4 (13%)
Preventability (Schumock and Thornton scale)	Non-preventable	2 (20%)	12 (23%)	13 (27%)	16 (53%)
	Probably preventable	5 (50%)	23 (44%)	23 (48%)	9 (30%)
	Definitely preventable	3 (30%)	17 (33%)	12 (25%)	5 (17%)

Table 3: Causality, avoidability and preventability of adverse drug reactions, at baseline and 3 months follow-up in patients who received standard care (control group) and patients who received the ISP intervention added to standard care (intervention group).

group than in the control group (p = 0.022). Although not significantly different, we detected four times as many gastrointestinal (n = 8 vs n = 2) and musculoskeletal disorders (n = 9 vs n = 2) in the intervention group than in the control group (Table 5).

4. Discussion

This study shows that physicians and an ISP team were able to detect and manage moderately severe (level 4) ADRs. The addition of an ISP team to standard care

Table 4. Frequency of adverse drug reactions (ADRs) by drug class at baseline and 3 months.

		Control group (n = 76)	Intervention group (n = 66)	P-value
Total number of ADRs at baseline		10	48	
Antihypertensives	ATC-C03, C07, C08, C09	2	12	0.002
Benzodiazepine derivatives	ATC-N05B	4	9	0.084
Analgesics (non-opioids and opioids)	ATC-N02	3	6	0.210
Urologicals	ATC-G04	3	6	0.210
Drugs used in diabetes	ATC-A10	0	7	0.004
Lipid modifying agents	ATC-C10	0	7	0.004
Antithrombotic agents	ATC-B01	0	6	0.007
Antidepressants	ATC-N06A	2	3	0.537
Antipsychotics	ATC-N05A	2	2	0.886
Total number of ADRs at 3 months		52	30	
Benzodiazepine derivatives	ATC-N05B	11	8	0.681
Antihypertensives	ATC-C03, C07, C08, C09	13	4	0.043
Drugs used in diabetes	ATC-A10	9	4	0.233
Urologicals	ATC-G04	7	5	0.727
Lipid modifying agents	ATC-C10	8	3	0.184
Analgesics (non-opioids and opioids)	ATC-N02	6	5	0.943
Antithrombotic agents	ATC-B01	8	2	0.082
Antidepressants	ATC-N06	2	3	0.537
Antipsychotics	ATC-N05A	2	2	0.886

Table 4: Frequency of adverse drug reactions (ADRs) by drug class at baseline and 3 months in patients who received standard care (control group) and patients who received the ISP intervention added to standard care (intervention group). Since ADRs could be caused by drugs from multiple drug classes, the sum of numbers in each column sum is greater than the total number of reactions.

Table 5. Types of adverse drug reactions (ADRs) at baseline and 3 months.

	Control group (n = 76)	Intervention group (n = 66)	P-value
Total number of ADRs at baseline	10	48	
Dizziness/light headedness/risk of falling	4	19	<0.001
Confusion/cognitive impairment	5	9	0.162
Gastrointestinal disorders (including bleeds)	0	8	0.002
Musculoskeletal disorders	0	7	0.004
Drowsiness	1	5	0.065
Other	0	6	0.007
Total number of ADRs at 3 months	52	30	
Dizziness/light headedness/risk of falling	21	8	0.022
Confusion/cognitive impairment	5	8	0.256
Gastrointestinal disorders (including bleeds)	8	2	0.083
Drowsiness	5	5	0.818
Musculoskeletal disorders	9	2	0.051
Other	4	5	0.576

Table 5: Types of adverse drug reactions (ADRs) at baseline and 3 months in patients who received standard care (control group) and patients who received the ISP intervention added to standard care (intervention group). Since ADRs could be caused by drugs from multiple drug classes, the sum of numbers given is greater than the total number of reactions.

resulted in significantly more mild and moderately severe (lever 1–3) ADRs being detected and treated during an outpatient visit ($p < 0.001$). Moreover, 3 months after the outpatient visit, significantly fewer ADRs were detected in patients from the intervention group than in patents from the control group ($p = 0.006$). Notably, there were fewer complaints of dizziness and falls ($p = 0.022$) and fewer ADRs related to antihypertensive drugs ($p = 0.043$) than in the control group.

An important finding is that moderately severe ADRs (level 4) were detected by both the physicians and the ISP-team, and mild and moderately severe (level 1–3) ADRs were more frequently detected by the ISP-team. Time-constraints, a primary focus on cognitive decline, indifference for less severe ADRs, high workload or inadequate pharmacovigilance education could be influencing factors.

To our knowledge, this is the first study that has evaluated the clinical effects of an intervention to detect ADRs in patients attending an outpatient clinic. While some student-led studies have evaluated the effect of students in detecting and reporting ADRs [30–32], or in assessing already reported ADRs [33], no studies have assessed the ability of students to detect and treat ADRs.

Studies that have evaluated the effects of physician- or pharmacist-led interventions have predominantly focused on improving inappropriate prescribing and reducing the risk of ADR-related hospital admissions or emergency department visits. Although these interventions are effective in reducing inappropriate prescribing, only a few reduce hospital admissions and emergency department visits, and most are not cost-effective [34,35]. Studies evaluating the effects of interventions specifically targeting ADRs have reported an increased detection of ADRs, resulting in

optimized treatment [36]. To our knowledge, no study has evaluated the outcome of this optimized treatment.

Although we found a comparable number of patients with ADRs as reported in an earlier study, in this elderly outpatient clinic the studied patients had more ADRs (median 2 ADR/patient) [37]. We also detected more ADRs than reported in an earlier study of patients with cognitive decline, although the types of ADRs and the drugs involved were similar [11]. This higher prevalence of ADRs might be due to the older age of our study population (mean 78 years), the thorough and proactive medication and ADR interview with a caregiver present, and the focus of the ISP team on mild and moderately severe ADRs, which are frequently missed.

Our study had some strengths and limitations. The main strengths of this study lie in the integration of the ISP team in an existing memory outpatient clinic, which increased the external validity of the study. Moreover, this approach has many educational benefits for participating students – during the patient interview students gain awareness and relevant clinical pharmacovigilance knowledge, which could lead to a greater awareness of potential medication problems in the future. The controlled clinical trial design with a 3-month follow-up allowed us to detect, manage, and evaluate the effects of interventions targeting specific ADRs in the two groups. Another strength of our study is the relatively low cost of the student-led teams compared with most physician- or pharmacist-led interventions in community dwelling outpatients, which are often not cost-effective [38,39]. The teams consisted of healthcare students or student-coordinators (all unpaid) who were only supervised (10-minutes per patient) by a clinical pharmacologist once during the entire process. A final strength is the scalability of this project. Although the pilot project only included one outpatient clinic, more outpatient clinics have been added to our program. With students from the LC-SRC and interns in abundance, it will be possible to have ISP teams in most outpatient clinics. Although this pilot is an extra-curricular event, we have proposed to make it part of the master program in the participating studies.

Our study also had a number of potential limitations. First, the follow-up of ADRs at 3 months was conducted by telephone interview with the patient and relative or caregiver. Since 52% of patients were diagnosed with dementia, it is possible that the number of ADRs was underestimated. We tried to address this limitation by having a caregiver to be present. Another limitation of the follow-up interview is that only subjective ADRs could be analyzed. Without clinical assessment, minor clinical abnormalities not yet causing patient symptoms, such as electrolyte imbalances, decline in kidney function or asymptomatic orthostatic hypotension, would have been missed. A third limitation is the significantly ($p = 0.026$) younger age of patients in the intervention group (mean 77.6, SD 4.8) than of patients in the control group (mean 79.5, SD 5.1), because more patients in the intervention group declined to participate at the 3-month follow-up. We would have expected the younger patients of the intervention group to have had fewer ADRs. A fourth limitation is the non-significant higher level of patients living alone in the intervention group (n = 30, 45.5%) than of patients in the control group (n = 24, 31.6%). A subgroup analysis did not find any significant or relevant effects between patients living alone or living in company. A final limitation is that ADRs are necessarily identified on the basis of clinical judgment. To overcome possible between-observer differences, all suspected ADRs were assessed for causality by the attending physician and a clinical pharmacologist, using two validated instruments (Naranjo and WHO), which showed a high degree of agreement (96%). Nevertheless, it is impossible to be absolutely certain of a causal link between a drug and an ADR.

Taking these strengths and limitations into account, we conclude that an inter-professional team of healthcare students added to standard care is a relevant intervention to increase the detection and management of ADRs in an outpatient clinic. This resulted in patients having fewer mild and moderately severe ADRs at a 3-month follow-up. As students are keen to participate in student-led clinics and are willing to support physicians in their obligations to detect and treat ADRs, the program could be incorporated in multiple settings, such as other geriatric clinics, clinics after surgery, neurology, or revalidation. The results also suggested that the ISP team detected (92%) and managed (93%) most of the ADRs. Thus, the task of detecting and treating ADRs could potentially be assigned to an ISP team, relieving physicians in this time-consuming task.

The concept of a (student-run) inter-professional student team focusing on the detection and management of ADRs in outpatient clinics should be of interest to other healthcare professionals and educators, since detecting and treating ADRs and training students in pharmacovigilance are universal challenges. In these teams, students have the opportunity to learn about pharmacovigilance and have responsibility for real patients while working in an inter-professional setting, more ADRs are detected, which leads to fewer ADRs in the long term, and healthcare professionals have more time to focus on primary outpatient goals.

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Author contributions

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MC Richir, R Sultan, and J Tichelaar performed the research. MO Reumerman, MC Richir, and R Sultan analyzed the data.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. Eur Respir J. 2014 Oct;44(4):1055–1068.
2. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. Br J Clin Pharmacol. 2015;80(4):796–807.
3. Field TS, Jh G, Avorn J, et al. Risk factors for adverse drug events among nursing home residents. Arch Internal Med. 2001 Jul 9;161 (13):1629–1634.
4. Thomsen LA, Winterstein AG, Søndergaard B, et al. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007 Sep;41 (9):1411–1426.
5. Dormann H, Criegee-Rieck M, Neubert A, et al., Lack of awareness of community-acquired adverse drug reactions upon hospital admission: dimensions and consequences of a dilemma. Drug Saf. 2003;26(5):353–362.
   - • **Study that highlights the lack of awerensess and consequences of not detecting adverse drug reactions**
6. Roulet L, Ballereau F, Hardouin JB, et al. Assessment of adverse drug event recognition by emergency physicians in a French teaching hospital. Emer Med J. 2013;30(1):63–67.
7. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19–31.
8. Irving G, Neves AL, Dambha-Miller H, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. BMJ Open. 2017;7:e017902.
9. Keijsers CJ, van Hensbergen L, Jacobs L, et al. Geriatric pharmacology and pharmacotherapy education for health professionals and students: a systematic review. Br J Clin Pharmacol. 2012 Nov;74(5):762–773.
   - • **Systematic review showing the lack op geriatric pharmacotherapy education**
10. Brinkman D, Tichelaar J, Graaf S, et al. Do final-year medical students have sufficient prescribing competencies? A systematic literature review. Br J Clin Pharmacol. 2018 Apr;84(4):615–635.
11. Kanagaratnam L, Dramé M, Trenque T, et al. Adverse drug reactions in elderly patients with cognitive disorders: a systematic review. Maturitas. 2016;85:56–63.
12. Granas A, Halvorsen K, Wendelbo J, et al. Interdisciplinary medication review to improve pharmacotherapy for patients with intellectual disabilities. Int J Clin Pharm. 2019 Dec;41(6):1516–1525.
13. Onder G, Gambassi G, Scales CJ, et al. Adverse drug reactions and cognitive function among hospitalized older adults. Eur J Clin Pharmacol. 2002;58(5):371–377.
14. Reumerman MO, Richir MC, Domela Nieuwenhuis PM, et al. The clinical and educational outcomes of an inter-professional student-led medication review team, a pilot study. Eur J Clin Pharmacol. 2020;77(1):117–123. Pilot study that describes the concept and educational results of an ISP-team intervention.
15. Sultan R, van den Beukel TO, Reumerman MO, et al. An inter-professional student-run medication review program: the clinical STOPP/START-based outcomes of a controlled clinical trial in a geriatric outpatient clinic. Clin Pharmacol Ther. 2022;111(4):931–938.
   - •• **Controled clinical trial focusing on optimising medication by an ISP-team**
16. Rhodius-Meester HFM, van de Schraaf SAJ, Peters MJL, et al. Mortality risk and its association with geriatric domain deficits in older outpatients: the Amsterdam ageing cohort. Gerontology. 2021 Jan;13:1–8.
17. Schutte T, Prince K, Richir M, et al. Opportunities for students to prescribe: an evaluation of 185 consultations in the student-run cardiovascular risk management programme. Basic Clin Pharmacol Toxicol. 2018 Feb;122(2):299–302.
18. Schutte T, Tichelaar J, Donker E, et al. Clarifying learning experiences in student-run clinics: a qualitative study. BMC Med Educ. 2018;18(1):244.
19. Dekker RS, Schutte T, Tichelaar J, et al. A novel approach to teaching pharmacotherapeutics–feasibility of the learner-centered student-run clinic. Eur J Clin Pharmacol. 2015;71(11):1381–1387.
20. Schutte T, Tichelaar J, Dekker RS, et al. Motivation and competence of participants in a learner-centered student-run clinic: an exploratory pilot study. BMC Med Educ. 2017 Jan 25;17(1):23.
21. Maanen D-V, Clara A, van Marum RJ, et al. Prescribing optimization method for improving prescribing in elderly patients receiving polypharmacy: results of application to case histories by general practitioners. Drugs Aging. 2009;26(8):687–701.
22. Gallagher P, Ryan C, Byrne S, et al. STOPP (screening tool of older person's prescriptions) and start (screening tool to alert doctors to right treatment). consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.
23. Mull HJ, Nebeker JR, Shimada S, et al. Consensus building for development of outpatient adverse drug event triggers. J Patient Saf. 2011 Jun;7(2):66–71.
24. Thevelin S, Spinewine A, Beuscart J, et al. Development of a standardized chart review method to identify drug-related hospital admissions in older people. Br J Clin Pharmacol. 2018 Nov;84 (11):2600–2614.
25. The use of the WHO-UMC system for standardized case causality assessment. World Health Organization (WHO) — Uppsala monitoring centre. Last accessed on 2020 Nov 23]. Available from 2020 Nov 23: http://www.who-umc.org/Graphics/24734.pdf
26. Naranjo C, Busto U, Sellers E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239–245.
27. Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990;228(2):83–90.
28. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538.
29. Hartwig SC, S J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992 Sep;49(9):2229–2232.
30. Reumerman M, Tichelaar J, Richir MC, et al. Medical students as adverse drug event managers, learning about side effects while improving their reporting in clinical practice. Naunyn Schmiedebergs Arch Pharmacol. 2021;394(7):1467–1476.
31. Sullivan KM, Spooner LM. Adverse-drug-reaction reporting by pharmacy students in a teaching hospital. Am J Health Syst Pharm. 2008;65(12):1177–1179.
32. Reumerman MO, Tichelaar J, Richir MC, et al. Medical students as junior adverse drug event managers facilitating reporting of ADRs. Br J Clin Pharmacol. 2021;87(12):4853–4860.
33. Schutte T, Tichelaar J, Reumerman MO, et al. Feasibility and educational value of a student-run pharmacovigilance programme: a prospective cohort study. Drug Saf. 2017;40(5):409–418.

34. Huiskes VJ, Burger DM, van den Ende Ch, et al. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017 Jan 17;18(1):5.
35. Khalil H, Bell B, Chambers H, et al. Professional, structural and organisational interventions in primary care for reducing medication errors. Cochrane Database Syst Rev. 2017 Oct 4;10(10):CD003942.
36. Gabe ME, Murphy F, Davies GA, et al. Medication monitoring in a nurse-led respiratory outpatient clinic: pragmatic randomised trial of the west wales adverse drug reaction profile. PLoS One. 2014 May 5;9(5):e96682.
37. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother. 2011 Jul;45(7–8):977–989.
38. Pacini M, Smith R, Wilson E, et al. Home-based medication review in older people: is it cost effective? PharmacoEconomics. 2007;25 (2):171–180.
39. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care–the POLYMED randomised controlled trial. Age Ageing. 2007 May;36(3):292–297.