Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies

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ABSTRACT

BACKGROUND: Drug-related problems (DRPs) are prevalent among chronic kidney disease (CKD) patients. However, little is known about their severity and management by community pharmacists.

OBJECTIVES: To (a) describe the prevalence of DRPs by severity level in CKD patients and (b) assess the effect of a training-and-communication network program in nephrology (ProFiL) on these DRPs.

METHODS: This is a secondary analysis of a cluster randomized controlled trial evaluating the effect of the ProFiL-program. In 6 CKD clinics, patients at CKD stage 3 or 4 and their community pharmacists were recruited and assigned to the ProFiL group or a usual care (UC) group. Using validated criteria, 2 pharmacists identified DRPs and assessed their severity at baseline and after 12 months. The mean annual change in the number of DRPs per patient by severity level was assessed using a 2-level multivariable linear mixed-effects model.

RESULTS: A total of 494 pharmacists and 442 patients participated. At baseline, the prevalence (mean number of DRPs per patient [SD]) of mild DRPs (e.g., requiring dosage adjustment) and moderate DRPs (e.g., drug adherence requiring a monitoring plan) were 0.55 (0.98) and 1.04 (1.51), respectively. After 12 months, an unadjusted incremental annual reduction of 0.34 moderate DRPs (95% CI = -0.66 to -0.01) was observed in the ProFiL group compared with the UC group. After adjustment, no between-group differences were observed.

CONCLUSIONS: Among patients followed in CKD clinics, most DRPs have a moderate severity requiring specific monitoring by pharmacists. The benefit of continuing education programs, such as ProFiL, to reduce moderate DRPs remains to be determined.

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What is already known about this subject

- Chronic kidney disease (CKD) patients are at high risk of suffering drug-related problems (DRPs), not only because of their decreased kidney function but also because they receive multiple medications prescribed simultaneously by different physicians.
- Nonadherence, adverse events, drug interactions, and inappropriate doses are DRPs frequently observed in CKD patients.

What this study adds

- The most frequently observed DRPs in patients with CKD are nonadherence to drug therapy and the use of drugs not recommended or requiring a dose adjustment in CKD.
- Nonadherence is deemed a moderately severe DRP, which requires the community pharmacist to implement a monitoring plan and follow-up.
- A training-and-communication network program in nephrology intended for community pharmacists may serve to improve the detection and management of moderately severe DRPs in CKD patients.

Chronic kidney disease (CKD) patients are medically complex cases. They take a mean of 10 to 13 medications and are followed by several physicians.[1] These factors increase the patients' risk of drug-related problems (DRPs).[2,3] In CKD patients, the prevalence of DRPs has been estimated at 2.8 (95% confidence interval [CI] = 2.3-3.2) DRPs/patient for creatinine clearance 30-59 mL/min[4]; and 4-8 DRPs per patient on hemodialysis.[4,5]

Common DRPs in CKD are adverse events, drug interactions, and inappropriate doses; these DRPs result from decreased kidney function.[2,3,6] The mortality rate associated with inappropriate drug use is 40% higher in patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 compared with patients without CKD.[7] CKD patients also demonstrate poor adherence to pharmacotherapy, particularly cardiovascular medications.[8] A large variation has been documented in the prevalence of nonadherence in end-stage renal disease (3%-80%), which may be partly explained by different definitions and measurements of nonadherence.[9] Nevertheless, the information about the severity of these DRPs is still limited.

In the hospital context, researchers have sought to measure DRP severity in terms of clinical and economic consequences.[10,11] So far, no information is available on the severity of DRPs detected among CKD patients followed in an ambulatory setting where community pharmacists play a crucial role in DRP detection and management.[12] Moreover, nothing is known about the effect of community pharmacists' interventions on DRP prevalence by severity level.

The objectives of this study were to (a) describe DRP prevalence according to severity in CKD nonhemodialysis patients

followed in 6 ambulatory CKD clinics, and (b) assess the effect of a training-and-communication network program in nephrology for community pharmacists on DRP prevalence, when classified by severity level.

Methods

Design, Setting, and Participants

This project is a secondary analysis of a cluster randomized controlled trial evaluating the effect of a training-and-communication program in nephrology for community pharmacists, the ProFiL program, on the quality of medication use in CKD patients. The ProFiL study has been fully described elsewhere.[13] This project was approved by the ethics and research board of the Centre hospitalier de l'Université de Montréal. Participating patients and community pharmacists signed an informed consent form.

In short, potentially eligible patients and their community pharmacists in 6 CKD clinics in Quebec, Canada, were invited to participate in the study. Eligible patients met the following criteria: (a) aged ≥ 18 years; (b) an eGFR of 30-59 mL/min/1.73m^2 (stage 3 CKD) or an eGFR of 15-29 mL/min/1.73m^2 (stage 4 CKD), as determined by the most recent laboratory result available in the CKD clinic; (c) speaking English or French; (d) followed by an eligible community pharmacy; and (e) agreeing to be followed by the same community pharmacy for the duration of the study. To be eligible, the pharmacy had to meet the following criteria: If the pharmacy was open 7 days per week, participating pharmacists had to cover at least 35 hours per week for a workload of < 250 prescriptions per day or at least 60 hours per week for a workload of > 250 prescriptions per day; if the pharmacy was open fewer than 7 days per week, participating pharmacists had to cover at least 50% of the working hours.

Each cluster, comprising a community pharmacy with pharmacists and patients, was randomly assigned to either the ProFiL group or the control group using a 2:1 ratio (2 ProFiL; 1 usual care [UC]). Pharmacies serving patients from more than 1 clinic were randomized only once. During the 12 months of the study, ProFiL pharmacists had access to the ProFiL program, while UC pharmacists continued to provide their usual pharmaceutical care.

ProFiL Program

ProFiL is a training-and-communication network program in nephrology for community pharmacists that consists of a web-based training program supported by a clinical guide, a discussion forum, the provision of a clinical summary, and a facilitated access to a pharmacist with expertise in nephrology.[13] The training program proposed a systematic approach to prevent, detect, and manage clinically significant DRPs featured in the Pharmacotherapy Assessment in Chronic Renal Disease (PAIR) criteria (see the Identification of DRPs section for a complete description).[14]

The systematic approach was based on the analysis of all relevant information available to ProFiL pharmacists, including the clinical summary. The clinical summary was completed for each patient by staff at the CKD clinic and sent to the community pharmacists to facilitate the detection of DRPs. It included a list of patients' health problems, their eGFRs according to the Chronic Kidney Disease Epidemiology Collaboration equation,[15] and a list of their medications as recorded in the CKD clinic chart. During the study, community pharmacists were encouraged to consult a nephrology pharmacist when needed.

In the UC group, the clinical summary was completed but not sent to the community pharmacists. UC pharmacists did not have access to the ProFiL program, but they could contact the CKD clinic as usual to obtain relevant clinical information or suggest changes to pharmacotherapy.

Identification of DRPs

Study patients were evaluated at baseline (T0) and 12 months later (T12). For each patient, DRPs were identified at T0, using the information collected for the year preceding recruitment; and at T12, with the information collected during the study. Two pharmacists independently identified DRPs in 442 study patients based on information from their community pharmacy medication renewal charts, their clinical summaries, and their use of over-the-counter (OTC) medications and natural health products as documented in a telephone interview.

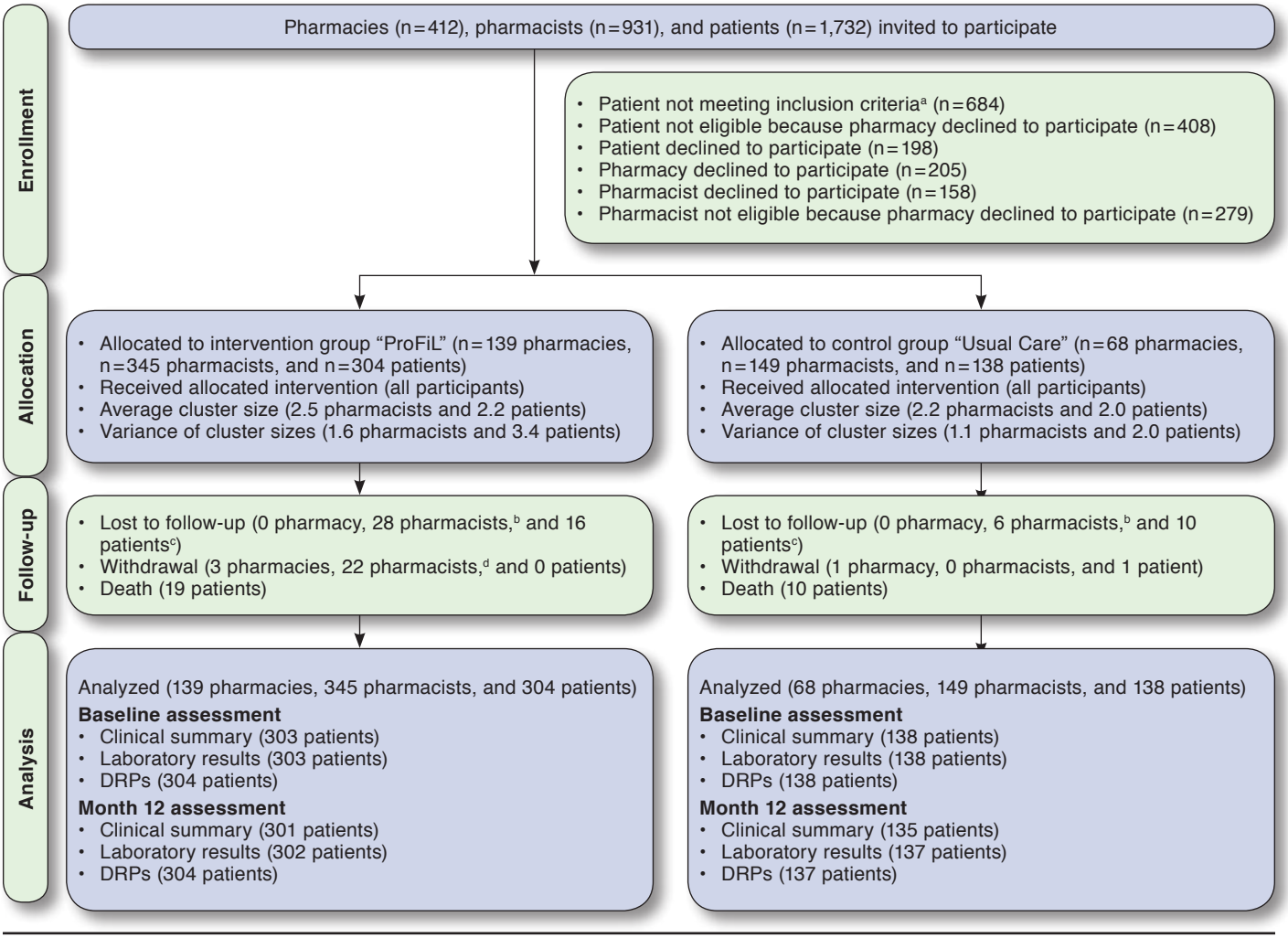
Pharmacists detected DRPs using a systematic approach based on the PAIR criteria—a list of 50 DRPs deemed clinically significant and requiring a community pharmacist's intervention.[14] The PAIR criteria have shown good interrater reliability, with kappa coefficients varying from 0.80 to 1.00 and high test-retest reliability, with kappa coefficients from 0.74 to 1.00.[14] Using these criteria, DRPs were classified into 7 categories: (1) use of drugs not recommended or requiring a dose adjustment in CKD; (2) nonadherence to drug therapy; (3) uncontrolled blood pressure; (4) hypoglycemia secondary to sulfonylureas; (5) drug interactions and/or drug used inappropriately; (6) smoking; and (7) use of OTC medications and natural health products not recommended in CKD. When an evaluation was discordant, the pharmacists were required to discuss it and reach a consensus.[16] These evaluations were not transmitted to community pharmacists.

Based on the evaluations conducted at T0 and T12, DRPs were classified into three categories: (1) "maintained" if detected at T0 and T12; (2) "resolved" if detected only at T0; and (3) "new" if detected only at T12.

Assessment of DRP Severity

The severity of the identified DRPs was assessed using the Severity Categorization for Pharmaceutical Evaluation (SCOPE) criteria.[17] According to these criteria, severity is determined by the intensity of the pharmaceutical intervention required to appropriately manage DRPs. These criteria propose 3 categories

FIGURE 1 Flowchart of the ProFiL Study



[a]Patient not meeting inclusion criteria: eGFR < 15 mL/min/1.73m² (n = 325); eGFR ≥ 90 mL/min/1.73m² (n = 97); doesn't have Quebec health insurance plan (n = 91); unable to manage medication (n = 55); unable to speak either English or French (n = 49); withdrawal before entering the study (n = 26); obtains medications from several pharmacies (n = 19); unable to understand the study (n = 18); hospitalized (n = 4).
[b]Lost to follow-up: changed pharmacy (n = 34).
[c]Lost to follow-up: changed pharmacy (n = 10); withdrawal of pharmacy (n = 9); dialysis (n = 7).
[d]Withdrawal: lack of time (n = 17); withdrawal of pharmacy (n = 3); unsatisfied (n = 2).
DRPs = drug-related problems; eGFR = estimated glomerular filtration rate.

of severity (mild, moderate, and severe) with 2 levels of interventions per category.

Level I interventions (mild severity) consist of preventing a DRP's occurrence through patient education or the transmission of relevant clinical information to the clinician. At level II (mild severity), a 1-time intervention, such as a pharmaceutical opinion issued to the treating physician, is required to resolve a DRP. The pharmaceutical opinion is a reasoned assessment, given under the pharmacist's legal authority on the patient's medication history or on the therapeutic value of a prescribed treatment or combination of treatments.[18] At level III (moderate severity), pharmacists need to implement specific monitoring and a follow-up plan to manage a DRP. When a DRP is more severe, patients need to be referred to their physician or CKD clinic as soon as possible (at level IV, moderate); need to be referred immediately to the emergency room or to their physician (at level V, severe); or require immediate assistance, in which case 911 should be called (at level VI, severe). The test-retest reliability and the interrater reliability of the SCOPE criteria varied from 0.79 to 0.90 and 0.72 to 0.82, respectively.[17]

The SCOPE criteria were applied by 1 of 3 pharmacists to all DRPs identified at T0 and/or T12. Considering the good

TABLE 1 Characteristics of Participants

	ProFiL Group	Usual Care Group
Patient characteristics		
Number	304	138
Age (years), mean (SD)	71.9 (12.0)	71.2 (12.5)
Men, n (%)	179 (58.9)	83 (60.1)
Race, n (%)[a]		
Caucasians	280 (92.1)	118 (85.5)
Other	18 (6.0)	16 (11.6)
Highest level of education attained, n (%)[a]		
Primary or secondary	213 (71.5)	74 (55.2)
College or university	85 (28.5)	60 (44.8)
Occupation, n (%)[a]		
Employed	48 (16.6)	24 (18.6)
Retired	226 (77.9)	102 (79.1)
Other	16 (5.5)	3 (2.3)
Total family income before taxes, n (%)[a]		
<$30,000/year	133 (52.6)	56 (53.3)
≥$30,000/year	120 (47.4)	49 (46.7)
Severity of chronic kidney disease, n (%)[a]		
Stage 1 (eGFR ≥ 90 mL/min/1.73m^2)	0 (0.0)	0 (0.0)
Stage 2 (eGFR 60-89 mL/min/1.73m^2)	1 (0.3)	1 (0.7)
Stage 3 (eGFR 30-59 mL/min/1.73m^2)	89 (29.5)	48 (35.0)
Stage 4 (eGFR 15-29 mL/min/1.73m^2)	202 (66.5)	85 (61.6)
Stage 5 (eGFR < 15 mL/min/1.73m^2)	10 (3.3)	3 (2.2)
Average renal function, mean (SD)[b]		
eGFR (mL/min/1.73m^2)	26.8 (9.3)	28.2 (10.7)
Creatinine (umol/L)	213.3 (73.0)	210.2 (73.4)
Body mass index (kg/m^2), mean (SD)[c]	30.4 (6.3)	29.3 (6.7)
Comorbidities, n (%)[d]		
Hypertension[e]	283 (95.3)	130 (94.9)
Dyslipidemia[f]	223 (75.1)	100 (73.5)
Type I diabetes[g]	11 (3.7)	4 (3.0)
Type II diabetes[e]	160 (53.5)	65 (48.1)
Coronary artery disease[h]	130 (45.1)	55 (41.4)
Comorbidities, n (%)[d]		
Anemia[i]	160 (54.8)	77 (57.5)
Phosphocalcic imbalance[j]	138 (48.1)	60 (45.5)
Hyperkalemia[k]	67 (23.0)	38 (28.6)
Nonsmoker, n (%)[l]	262 (89.4)	120 (92.3)
On pill dispenser prepared by community pharmacists, n (%)[m]	132 (45.1)	56 (41.8)
Community pharmacy characteristics		
Number	139	68
Pharmacist workload, n (%)		
≤30 prescriptions/hour/pharmacist	94 (67.6)	44 (64.7)
>30 prescriptions/hour/pharmacist	45 (32.4)	24 (35.3)
Number of prescriptions dispensed per day, mean (SD)	440.1 (235.8)	457.9 (245.5)
Weekly opening hours for customer service, mean (SD)[b]	80.2 (14.9)	81.8 (16.5)
Pharmacy floor space (ft^2), n (%)[a]		
<1,000	7 (5.7)	3 (5.0)
1,000-2,500	18 (14.8)	9 (15.0)
2,501-5,000	22 (18.0)	11 (18.3)
>5,000	75 (61.5)	37 (61.7)
Pharmacist characteristics		
Number	345	149
Sex, n (%)		
Women	236 (68.4)	100 (67.1)
Men	109 (31.6)	49 (32.9)
Pharmacist status, n (%)		
Owner pharmacist	95 (27.5)	39 (26.2)
Salaried pharmacist	250 (72.5)	110 (73.8)
Year of graduation, n (%)[a]		
2001 or later	181 (53.6)	77 (54.2)
1991-2000	83 (24.6)	36 (25.4)
1981-1990	49 (14.5)	18 (12.7)
1980 or earlier	25 (7.4)	11 (7.7)

Missing data: [a]Numbers may not add to total number in study group, [b]3, [c]37, [d]several categories may be reported, [e]8, [f]9, [g]12, [h]21, [i]16, [j]13, [k]18, [l]19, and [m]15.
eGFR = estimated glomerular filtration rate; SD = standard deviation.

reliability of the SCOPE criteria, pharmacists did not have to reach a consensus on severity.

Statistical Analysis

Patient characteristics were described using means (standard deviation [SD]) for continuous variables and a number (proportion) for categorical variables. For each patient, the number of DRPs at each level of severity was computed at T0 and T12 as well as the change from baseline to the end of the study (T12-T0).

The mean number of mild, moderate, and severe DRPs per patient and the mean change from baseline to the end of the study were computed for the ProFiL group and the UC group. The between-group difference (ProFiL-UC) in mean change and the 95% CI were estimated using a 2-level (pharmacy and individuals) multivariable linear mixed-effects model[19-21] to take into account the clustering of data within the pharmacy and patient-level intracorrelation induced by repeated measures, all modeled as random effects. We also adjusted for covariables showing imbalance between the ProFiL and UC groups at baseline (patient: eGFR and highest level of education). Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and SPSS package 19 (SPSS, Chicago, IL).

Results

Baseline Patient Characteristics

Of the 1,732 patients invited to participate in the study, 442 were eligible and recruited; 304 were assigned to the ProFiL group and 138 to the UC group. Most excluded patients were not eligible because they did not meet the inclusion criteria (n = 684) or their pharmacy declined to participate (n = 408) (Figure 1).

TABLE 2 Number of DRPs by Severity Level at Baseline Based on the SCOPE Criteria

	Category and Level of Severity Based on SCOPE Criteria (%)[a]							
	Mild				Moderate			
PAIR DRPs Category, n (%)	Level I		Level II		Level III		Level IV	
Total[b]	**176**	**(19.6)**	**251**	**(28.0)**	**469**	**(52.3)**	**1**	**(0.1)**
Drugs not recommended in CKD[c]								
Acarbose	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)
NSAIDs	11	(6.3)	18	(7.2)	18	(3.8)	1	(100.0)
Biphosphonates	0	(0.0)	22	(8.8)	1	(0.2)	0	(0.0)
Metformin	0	(0.0)	17	(6.8)	1	(0.2)	0	(0.0)
Nitrofurantoin	0	(0.0)	8	(3.2)	0	(0.0)	0	(0.0)
Subtotal	**11**	**(6.3)**	**67**	**(26.7)**	**20**	**(4.3)**	**1**	**(100.0)**
Drugs requiring a dose adjustment in CKD[c]								
Anti-infectives	2	(1.1)	43	(17.1)	0	(0.0)	0	(0.0)
Allopurinol	0	(0.0)	11	(4.4)	0	(0.0)	0	(0.0)
Beta blockers	0	(0.0)	7	(2.8)	1	(0.2)	0	(0.0)
Others	4	(2.3)	26	(10.4)	0	(0.0)	0	(0.0)
Subtotal	**6**	**(3.4)**	**87**	**(34.7)**	**1**	**(0.2)**	**0**	**(0.0)**
Nonadherence to drug therapy[c]								
Antihypertensives	0	(0.0)	0	(0.0)	75	(16.0)	0	(0.0)
Antidiabetics	0	(0.0)	0	(0.0)	54	(11.5)	0	(0.0)
Hypolipemiants	0	(0.0)	2	(0.8)	30	(6.4)	0	(0.0)
Anemia	0	(0.0)	1	(0.4)	41	(8.7)	0	(0.0)
Phosphocalcic imbalance	0	(0.0)	1	(0.4)	71	(15.1)	0	(0.0)
Subtotal	**0**	**(0)**	**4**	**(1.6)**	**271**	**(57.8)**	**0**	**(0.0)**
Uncontrolled blood pressure[c]	2	(1.1)	0	(0.0)	114	(24.3)	0	(0.0)
Hypoglycemia secondary to sulfonylureas[c]	0	(0.0)	0	(0.0)	25	(5.3)	0	(0.0)
Drug interactions and/or drug used inappropriately[c]	20	(11.4)	58	(23.1)	13	(2.8)	0	(0.0)
Smoking[c]	38	(21.6)	0	(0.0)	2	(0.4)	0	(0.0)
OTC medications and natural health products not recommended in CKD[c]								
Antacids	36	(20.5)	10	(4.0)	2	(0.4)	0	(0.0)
Purgatives	3	(1.7)	3	(1.2)	0	(0)	0	(0.0)
Vitamin A	12	(6.8)	6	(2.4)	0	(0)	0	(0.0)
NSAIDs	19	(10.8)	4	(1.6)	12	(2.6)	0	(0.0)
Pseudoephedrine/phenylephrine	16	(9.1)	2	(0.8)	7	(1.5)	0	(0.0)
Vitamin C	8	(4.5)	7	(2.8)	2	(0.4)	0	(0.0)
Other natural health products	5	(2.8)	1	(0.4)	0	(0)	0	(0.0)
Subtotal	**99**	**(56.3)**	**33**	**(13.1)**	**23**	**(4.9)**	**0**	**(0.0)**

[a]No DRPs were considered severe (levels V or VI) according to the SCOPE criteria.
[b]Percentages are calculated on a total number (n) of 897 DRPs identified at baseline in 442 patients.
[c]Percentages are calculated on the total number (n) of DRPs identified at baseline in each severity level.
CKD = chronic kidney disease; DRPs=drug-related problems; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over the counter; PAIR = Pharmacotherapy Assessment in Chronic Renal Disease; SCOPE = Severity Categorization for Pharmaceutical Evaluation.

On the basis of their last laboratory test results available on their medical charts in the CKD clinic, all patients were CKD stage 3 or 4 when recruited. However, at T0 participants were reclassified at stage 2 (0.05%; n = 2), stage 3 (30.9%; n = 137), stage 4 (64.9%; n = 287), or stage 5 (2.9%; n = 13; Table 1). All recruited patients were included in the final analyses.

Most patients were elderly (mean age was 71 years old) and predominantly Caucasian. Approximately 60% were men. More ProFiL patients had an eGFR ≥ 29 mL/min/1.73m^2 (69.7% vs. 63.0%) and more UC patients reported college or university as their highest level of education (44.8% vs. 28.5%).

As for comorbidities, 95.3% of patients had hypertension, 75.1% had dyslipidemia, 53.5% had type II diabetes, and 54.8% had anemia. Almost 70% (67.6%) of participating pharmacies had a workload of ≤ 30 prescriptions/hour/pharmacist. Participating pharmacists were predominantly women, were salaried, and had graduated after the year 2000 (Table 1). No statistical analyses were performed on baseline characteristics of participants.

TABLE 3 Incremental Changes in the Mean Numbers of DRPs in ProFiL Patients by SCOPE Level of Severity

SCOPE Category and Level		T0 Mean (SD)		T12 Mean (SD)		Incremental Change in ProFiL Group Compared with UC Group Mean (95% CI)	
		ProFiL n = 304	UC n = 138	ProFiL n = 304	UC n = 138	Unadjusted	Adjusted
Mild	I	0.42 (0.73)	0.31 (0.59)	0.37 (0.89)	0.31 (0.76)	-0.05 (-0.21, 0.12)	-0.03 (-0.21, 0.14)[a]
	II	0.58 (0.98)	0.47 (0.96)	0.52 (1.23)	0.51 (1.29)	-0.11 (-0.36, 0.15)	-0.10 (-0.38, 0.17)[b]
	Subtotal	**1.00 (1.19)**	**0.78 (1.26)**	**0.88 (1.54)**	**0.81 (1.54)**	**-0.16 (-0.44, 0.13)**	**-0.12 (-0.43, 0.18)[c]**
Moderate	III	1.09 (1.56)	0.95 (1.39)	1.05 (1.84)	1.24 (2.31)	-0.34 (-0.66, -0.01)	-0.31 (-0.63, 0.02)[d]
	IV	0.00 (0.06)	0.00 (0.00)	0.04 (0.34)	0.04 (0.19)	0.00 (-0.06, 0.06)	0.01 (-0.06, 0.07)[e]
	Subtotal	**1.09 (1.56)**	**0.95 (1.39)**	**1.08 (1.86)**	**1.24 (2.32)**	**-0.33 (-0.65, -0.01)**	**-0.29 (-0.61, 0.03)[f]**
Total		**2.16 (2.10)**	**1.70 (2.02)**	**1.60 (1.79)**	**1.62 (1.79)**	**-0.48 (-0.82, -0.14)**	**-0.32 (-0.60, -0.06)[g]**

Note: No DRPs were considered to be level V or VI (severe).

[a]Adjusted for the interaction between study group and number of DRPs level I at baseline, eGFR, and level of education.

[b]Adjusted for the interaction between study group and number of DRPs level II at baseline, eGFR, and level of education.

[c]Adjusted for the interaction between study group and number of DRPs level I and II at baseline, eGFR, and level of education.

[d]Adjusted for the interaction between study group and number of DRPs level III, eGFR, and level of education.

[e]Adjusted for the interaction between study group and number of DRPs level IV, eGFR, and level of education.

[f]Adjusted for the interaction between study group and number of DRPs level III and IV at baseline, eGFR, and level of education.

[g]Adjusted for the number of DRPs at baseline, the interaction between study group and number of DRPs at baseline, and for patient's age, sex, highest level of education, and eGFR, as well as for pharmacists' being an associate clinician and receiving remuneration for pharmaceutical opinions.

CI = confidence interval; DRPs = drug-related problems; eGFR = estimated glomerular filtration rate; SCOPE = Severity Categorization for Pharmaceutical Evaluation; SD = standard deviation; T0 = baseline; T12 = after 12 months; UC = usual care.

Prevalence of DRPs by Severity Level

As reported in Table 2, 897 DRPs were identified at baseline in 442 patients. Regardless of the study group, the mean numbers of DRPs per patient (SD) according to SCOPE severity level were level I: 0.39 (0.69); level II: 0.55 (0.98); and level III: 1.04 (1.51; data not shown).

A total of 176 DRPs were classified as level I. Among these, 99 (56.3%) were associated with OTC medications not recommended for CKD, such as antacids (20.5%). Two hundred fifty-one DRPs were classified as level II. They were mostly associated with the use of drugs not recommended for CKD (67 [26.7%]), like biphosphonates (8.8%), or drugs requiring a dosage adjustment for CKD (87 [34.7%]), mainly anti-infectives (43 [17.1%]).

The majority of all DRPs observed (469) were classified as level III. They were mainly related to nonadherence to drug therapy (271 [57.8%]), particularly antihypertensives (75 [16%]) and uncontrolled blood pressure (114 [24.3%]). Only 1 DRP was deemed level IV, and no DRPs deemed level V or VI were found.

Effect of ProFiL Program on DRP Prevalence by Severity Level

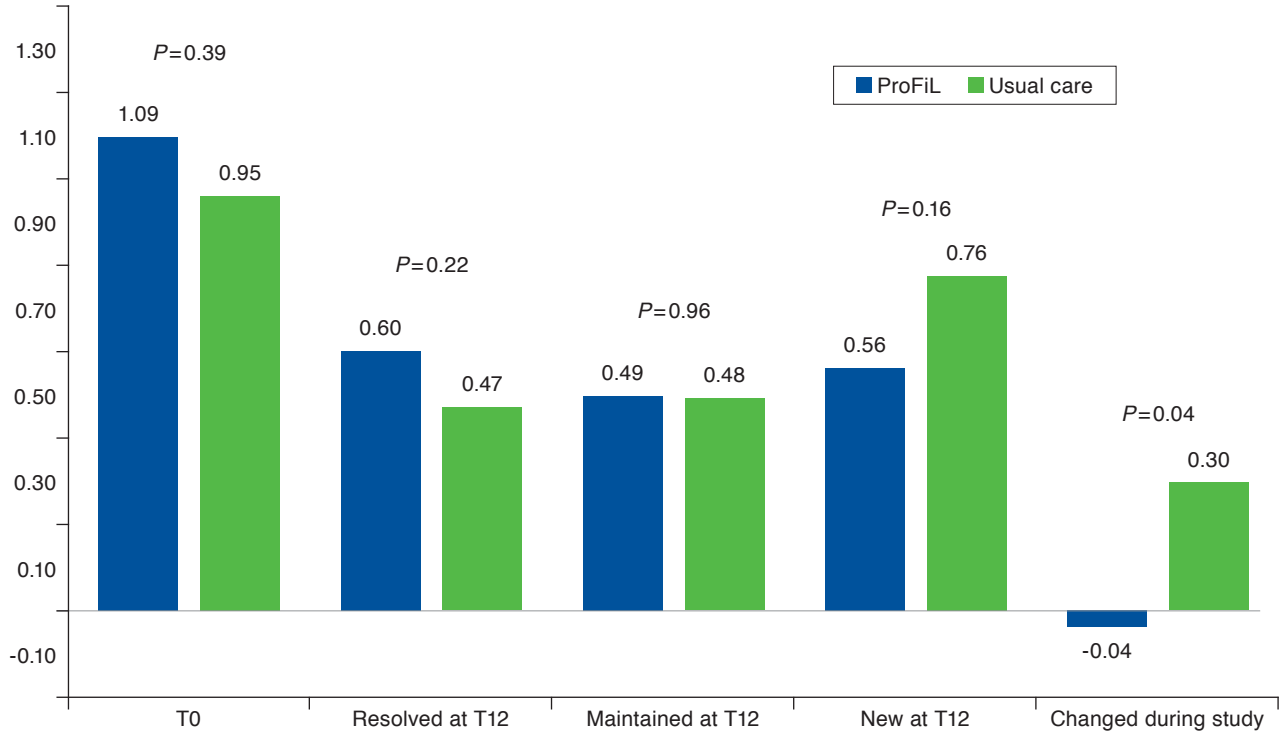
At baseline, the overall mean numbers of DRPs per patient were 2.16 (SD = 2.10) and 1.70 (2.02) in the ProFiL and UC groups, respectively (Table 3). After 12 months (T12), they were 1.60 (1.79) and 1.62 (1.79), respectively. The adjusted incremental change in the ProFiL group was equal to -0.32 DRPs/patient (95% CI = (-0.60 to -0.06), after adjusting for the number of DRPs at baseline, the interaction between the study group, and the number of DRPs at baseline and other potential confounders. When stratified by severity level, the unadjusted between-group difference was statistically significant only for a DRP severity of level III: -0.34 (95% CI = -0.66 to -0.01). After being adjusted for potential confounders, the results were not statistically significant (0.31, 95% CI = -0.63, 0.02). These results seemed mostly driven by a reduction in the number of new DRPs at level III in the ProFiL group after 12 months (Figure 2).

Discussion

The prevalence of DRPs in CKD patients followed by a multidisciplinary team of health care professionals in CKD clinics was high, with an average of approximately 2 DRPs per patient. The results of this study underscore the clinical significance of this finding, showing that approximately half of these problems had a moderate severity and required specific monitoring by community pharmacists. In this subanalysis, within each severity level, the ProFiL program was not associated with a statistically significant reduction in the number of DRPs.

The essential role of pharmacists in managing drug therapy in CKD patients (including adjusting medication dosage, monitoring laboratory test values, and educating patients) has been documented in 2 systematic reviews.[22,23] Their interventions reduced the rate of hospitalizations and the relative risk of end-stage renal disease.[24] Phosphate and anemia management also improved.[25,26] If the same were to apply to community pharmacists, the potential for optimizing medication use would be substantial and, as suggested by our study, potentially achievable. However, the involvement of

FIGURE 2 Mean Number of DRPs (Level III) at Baseline (T0) and Mean Number of DRPs Resolved, Maintained, and Newly Identified at 1 Year (T12) in the ProFiL and the Usual Care Groups



DRPs = drug-related problems.

community pharmacists in managing CKD patients followed-up in predialysis and outpatient dialysis centers is still limited.[22]

The overall results of the ProFiL study (Lalonde et al., 2017) have shown that with appropriate training and access to essential clinical data, the contribution of community pharmacists is significant and beneficial.[13] In this subanalysis, we observed that moderate DRPs (requiring monitoring) were less frequent in the ProFiL group after 12 months. The significant nonadjusted effect of ProFiL over these DRPs was attenuated by 10% when adjusted and lost statistical significance, probably due to an insufficient statistical power. Therefore, the positive effect of ProFiL to reduce moderate DRPs remains unclear.

Based on the SCOPE criteria, nonadherence and uncontrolled blood pressure were deemed moderate DRPs, and their management requires community pharmacists to implement a specific monitoring plan. Similarly, in a study by Manley et al. (2005), 24% of DRPs required laboratory tests for appropriate monitoring.[5] It is important to consider that in our study, DRPs were identified based on the information available to community pharmacists, which excluded laboratory test results (except the eGFR).

However, shortly after the end of the study, most community pharmacists obtained access to laboratory tests. In Quebec, community pharmacists have recently been given such access through the Dossier Santé Québec.[27] Furthermore, under Bill 41, they can order laboratory tests for monitoring purposes.[28] It is therefore expected that, outside this study, community pharmacists will be able to detect and manage more DRPs by implementing vigilant laboratory monitoring.

Nonadherence was the most prevalent moderate DRP. It represents a major problem in health care and a barrier to achieving optimal CKD outcomes.[29-33] Nonadherence leads to a worsening condition, death, and increased costs,[30,34] particularly for elderly patients.[35,36] It is associated with uncontrolled hypertension and higher rates of mortality in hemodialysis patients.[37,38]

Several studies on nonadherence have highlighted that patients are concerned about polypharmacy and adverse events, and they do not discuss their medication beliefs and treatment priorities with physicians.[8,39] Other barriers include forgetfulness, lack of information or involvement in decision making, cost, complex regimens, and poor communication.[8] Community pharmacists are well positioned to address these barriers by implementing multifactorial strategies, including patient education and enhanced decision making. Optimal management of adherence requires frequent interactions

between pharmacists and patients to reinforce interventions.[40] In Quebec, medications are usually dispensed every 30 days,[41] and patients tend to go to only 1 pharmacy.[4] Again, the potential for community pharmacists to detect and improve adherence to medication is very important.

Evaluating DRP severity was useful to determine which DRPs require a more intense management by community pharmacists. This information might also be eventually helpful to develop remuneration models.[42] Pharmacists in some Canadian provinces, the United States, and Australia are now remunerated for medication reviews.[8,43,44] A recent systematic review of pharmacist-provided fee-for-service interventions found significant improvements in the achievement of blood pressure and low-density lipoprotein cholesterol goals; moreover, 58% of these studies demonstrated improved medication adherence.[45] Many of these studies targeted patients with hypertension, diabetes, or both and included a smoking cessation component. The ProFiL program included some of these elements, and our results suggest it may improve the prevention and management of moderate DRPs. But the efficacy of the ProFiL program in real life still needs to be demonstrated.

Limitations

To our knowledge, this is the first study to evaluate the prevalence of DRPs by severity level in the context of community pharmacies. It was carried out as part of a randomized trial involving CKD patients, and we used 2 validated sets of criteria to identify DRPs and assess their severity, which enhances the study's internal validity.

However, there are also some limitations to this study. First, the identification and severity assessment of DRPs was performed by trained pharmacists using information collected for a clinical trial, which might differ from a direct evaluation performed by community pharmacists when they meet with patients. Second, our analysis was performed as a secondary objective of the ProFiL study, so its statistical power was insufficient to determine the effect of the ProFiL program on DRPs, when stratified by severity. Finally, even though the observed DRPs are generally present in all CKD patients, these results might be applicable only to those patients regularly seeing a community pharmacist and followed in CKD clinics.

Conclusions

The prevalence of DRPs is high among CKD patients under the care of a multidisciplinary team, particularly for moderate DRPs requiring pharmacist monitoring. Continuing education programs, such as ProFiL, have the potential to improve medication use in this population by reducing the prevalence of DRPs. But a particular effect of ProFiL on DRPs when stratified by severity remains to be determined.

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DISCLOSURES

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Study concept and design were contributed by Quintana-Bárcena, Lord, and Lalonde. Quintana-Bárcena, Lord, and Lizotte were responsible for the data analysis, and Quintana-Bárcena and Berbiche performed the statistical analysis. The manuscript was written by Quintana-Bárcena and Lalonde and revised by Quintana-Bárcena and Lalonde, along with the other authors.

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