Exploring Co-dispensed Drug Use in Patients on Sevelamer or Polystyrene Sulfonate to Identify Potential Novel Binding Interactions: a Cross Sectional in Silico Study

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Abstract

Background

Sevelamer and polystyrene sulfonate are used for treating hyperphosphatemia and hyperkalaemia in chronic kidney disease patients. Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness.

Aim

The aim of this study was to explore co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions.

Method

In this *in silico* study, the 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate in the period 2000-2018 from the University Groningen IADB.nl database were extracted. Drugs dispensed to < 5% of patients, drugs not orally administered, drugs administered once daily before bedtime and drugs for which information on binding interactions with sevelamer or polystyrene was already available were excluded. The likelihood of an interaction (yes or no) of the included drugs was assessed based on pKa- and Log P values. For sevelamer, drugs with a pKa (acid) between 1.5 and 7.4 and or a Log P value > 2.0 were identified as potential interacting drug. For polystyrene sulfonate, drugs with a pKa (base) > 1.5 were identified as potential interacting drug.

Results

Of the top 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate, 22 and 27 potentially clinically relevant new interacting drugs were identified for sevelamer and polystyrene sulfonate respectively.

Conclusion

Several potentially relevant novel binding interactions for sevelamer and polystyrene sulfonate were identified based on dispensing data and assessment of chemical properties for which further interaction research is warranted.

Impacts Of Findings On Practice Statements

- Sevelamer and polystyrene sulfonate, resins used to treat hyperphosphatemia and hyperkalaemia in chronic kidney disease patients, may bind other drugs in the gastrointestinal tract decreasing their bioavailability and clinical effectiveness
- For sevelamer, 22 potentially clinically relevant new interacting drugs were identified based on dispensing data and pKa- and Log P-values
- For polystyrene sulfonate, 27 potentially clinically relevant new interacting drugs were identified accordingly.
- Further in vitro and in vivo interaction research is necessary to confirm these findings and to assess the clinical relevance

Introduction

Resins, such as sevelamer and polystyrene sulfonate, are often used for binding phosphate and potassium to treat hyperphosphatemia and hyperkalaemia, which can cause serious complications in patients with Chronic Kidney Disease (CKD) [1.2]. Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. CKD patients often use many different drugs, due to comorbidities such as cardiovascular diseases, diabetes mellitus, metabolic disorders, gout and anaemia. Most often prescribed drug groups are cardiovascular drugs, antidiabetic agents, drugs for acid related gastro-intestinal disorders, anti-gout preparations and agents for the treatment of mineral bone disorder [3, 4]. Due to the high number of prescribed drugs, the prevalence of potential drug-drug interactions in CKD patients is high, varying from 75 to 91% [5–9]. For instance phosphate binders, used by 85% of haemodialysis patients, show several drug-drug interactions in clinical practice [10, 11]. Sevelamer is the phosphate binder of first choice because it reduces mortality when used as an alternative or addition to calcium containing phosphate binders [10, 12]. Furthermore, the use of calcium containing phosphate binders needs to be restricted due to an increased risk of metastatic and vascular calcifications [2]. Sevelamer is a non-absorbed polymer, free of metal and calcium. It contains several amines separated by one carbon from the polymer backbone. The amines become partially protonated in the gastro-intestinal tract and interact with phosphate molecules through ionic and hydrogen binding. This binding decreases the bioavailability of phosphate and thereby decreases elevated serum phosphate concentrations. In addition to its phosphate-binding properties, sevelamer acts as a bile acid sequestrant and significantly reduces low-densitiy lipoprotein (LDL) cholesterol levels [13].

Polystyrene sulfonate (available as sodium or calcium salt) is a cation-exchanging resin that has been widely used for several decades as first-line therapy of mild chronic hyperkalaemia in patients with CKD [1, 2]. It lowers the plasma potassium concentration through exchange of potassium and sodium/calcium ions in the gastro-intestinal tract, mainly in the colon and partly in the small intestine. Polystyrene sulfonate itself is not absorbed from the gastro-intestinal tract [14,15].

Studies and case reports investigating binding interactions of sevelamer show that sevelamer binds to levothyroxine, ciprofloxacin, mycophenolic acid, tacrolimus, cyclosporine, vitamin D analoga, lipid soluble vitamins like vitamin A, E and K, folic acid, quetiapine and furosemide [11,13–23]. For polystyrene sulfonate, binding interactions have been described with lithium, quetiapine and levothyroxine [22,24,25]. Based on the chemical mechanism of the known binding interactions there are possibly many more drugs that bind to sevelamer and/or polystyrene sulfonate. The Summary of Product Characteristics (SmPC) of polystyrene sulfonate underlines this by discouraging taking other oral medication three hours before or after polystyrene sulfonate intake [26]. In the Netherlands, only the known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing

between drugs. However, this advice is difficult to accomplish in a patient group using on average 8 different drugs per day [3, 4]. In addition, nephrologists may not be aware of binding interactions of these resins with comedication and their clinical implications [11]. Therefore, more knowledge about potential binding interactions with sevelamer and polystyrene sulfonate is relevant for tailored management in clinical practice. To be able to identify clinically relevant binding interactions, co-dispensed drug use of patients using sevelamer and or polystyrene sulfonate should be investigated.

Aim

The aim of the present study was to explore co-dispensed drug use of patients on sevelamer or polystyrene sulfonate to identify drugs for which further interaction research is warranted based on their chemical properties.

Ethics approval

No ethics committee approval is needed for research using anonymous medical records. This study was conducted in accordance with the Declaration of Helsinki.

Method

Design and setting

This study used an *in silico* strategy to detect potential novel drug-drug interactions. In a cross sectional study, we used pharmacy dispensing data from the population-based University Groningen, IADB.nl prescription database [27,28]. The database comprises prescription drug dispensing data from more than 70 community pharmacies in the northern and eastern part of the Netherlands since 1994, covering a population of approximately 700,000 people. Prescription rates among this database population have been found to be representative for the Netherlands as a whole and the database is widely used in research [27]. The database includes demographic information such as date of birth and gender and medication information with Anatomical Therapeutic Chemical (ATC) codes, dispensing date, amount and dose dispensed, number of defined daily doses dispensed and period of drug coverage, i.e. the period of time in days for which the patient had drugs dispensed [27]. Due to a high patient pharmacy commitment in the Netherlands and sophisticated software, the medication records for each patient are virtually complete, except for over-the-counter drugs and medicines dispensed during hospitalization.

Study population and Outcome definition

From the IADB database all patients using sevelamer (ATC-code V03AE02) and/or polystyrene sulfonate (ATC-code V03AE01) for at least 90 days in a period of 12 months between 1st January 2000 to 31st December 2018 were selected. The different options for identification of co-dispensed drugs are graphically depicted in Fig. 1 using drugs A, B, C and D as examples. Drugs were identified as ‘co-dispensed’ when they were dispensed before the first/follow up date of dispensing sevelamer/polystyrene sulfonate and the use covered a period ending after the dispensing date of sevelamer/polystyrene sulfonate (drug A and B). Furthermore, all drugs, which were dispensed after the first/follow up dispensing date of sevelamer/polystyrene sulfonate, but before the last day of coverage with sevelamer/polystyrene sulfonate, were included (drug C and D).

The number of patients who received a drug which was co-dispensed with sevelamer/polystyrene sulfonate during the study period was extracted from the database. A co-dispensed drug in combination with sevelamer or polystyrene sulfonate was counted only once for every individual patient. Therefore, this number is further referred to as ‘unique drug-sevelamer/polystyrene sulfonate combination’.

Analysis

Patient characteristics

We determined the mean age (including standard deviation and range) of sevelamer/polystyrene sulfonate users on July first of each study year from 2000 to 2018. Because there were no relevant differences between these results, we only reported the age data of 2009, the middle of the study period, in the results section.

Top 100 co-dispensed drugs - first level of ATC classification

The 100 drugs most frequently co-dispensed with sevelamer or polystyrene sulfonate during the study period were categorized in the first ATC-class level. Therefore, we combined the number of unique drug-sevelamer/polystyrene sulfonate combinations within the defined ATC-class first level. Subsequently, we calculated the percentage by dividing this number by the total number of unique drug-sevelamer/polystyrene sulfonate combinations in the top 100.

Top 100 co-dispensed drugs

We determined the percentage of sevelamer/polystyrene sulfonate users who received each drug from the top 100 during the study period, by dividing the number of unique drug-sevelamer/polystyrene sulfonate combinations by the total number of patients using sevelamer/polystyrene sulfonate.

Drugs for which further interaction research is warranted

From the list of 100 most frequently co-dispensed drugs we excluded all drugs, which were registered in duplicate. For example, calcium carbonate and cholecalciferol were amongst the top 100 drugs included as mono-preparations as well as a combination product. In this case, we excluded the combination product. We also excluded drugs dispensed to < 5% of the patients and drugs not orally administered. Furthermore, we excluded drugs usually administered once daily at bedtime, since for this dosage regimen an interaction with sevelamer or polystyrene sulfonate is unlikely. Finally, all the drugs for which there is evidence for an interaction or evidence that there is no interaction based on literature were excluded (supplementary data) [14–26,30,31].

This resulted in a list of drugs co-dispensed with sevelamer or polystyrene sulfonate, the number of unique drug-sevelamer/polystyrene sulfonate combinations and the percentage of patients having received the combination during the study period.

Thereafter the likelihood of an interaction with sevelamer was assessed based on the pKa (acid) and Log P value of the drugs [31]. Drugs with a pKa (acid) between 1.5 and 7.4 and/or a Log P > 2.0 were identified as potentially binding to sevelamer. Drugs with a pKa (acid) between 1.5 and 7.4 are at least 50% negatively charged in the gastrointestinal pH range of 1.5 to 7.4. Drugs with a Log P value > 2.0 are associated with potential binding to colesevelam and because sevelamer also acts as a bile sequestrant a Log P value > 2.0 was used as parameter for identifying potential binding to sevelamer [34].

Drugs with a pKa (base) > 1.5 were identified as potentially binding to polystyrene sulfonate because these drugs are at least 50% positively charged in the gastrointestinal pH range of 1.5 to 7.4.

The drugs were categorized as 'Yes' (binding interaction expected) or 'No' (binding interaction not expected).

Results

From the IADB-data base, 1,083 patients using sevelamer and 716 patients using polystyrene sulfonate for at least 90 days in a period of 12 months between January 2000 and December 2018 were identified. The patient characteristics are depicted in Table 1.

Table 1
Patient characteristics

	Sevelamer N = 1,083	**Polystyrene sulfonate N = 716**
Age*, years (mean (sd) [range])	62 (17) [1–89]	58 (20) [10–95]
Gender (N (%))		
Male	619 (57)	471 (66)
Female	464 (43)	245 (34)
Duration S / PSP use, days (mean (sd) [range])	840 (759) [90-5247]	576 (628) [90-3813]
Unique drug-S/PSP combinations (N (%))		
< 10	278 (25.7)	293 (40.9)
11–20	403 (37.2)	275 (38.4)
21–30	226 (20.9)	95 (13.3)
31–40	115 (10.6)	41 (5.7)
41–50	37 (3.4)	10 (1.4)
> 50	24 (2.2)	2 (0.3)
* Age measured on 1th July 2009		
sd: standard deviation		
S: sevelamer		
PSP: polystyrene sulfonate		

Seven hundred and fifty-five different drugs were dispensed to the sevelamer users during this study period, which resulted in 20,801 unique drug-sevelamer combinations; 654 different drugs were dispensed to the polystyrene sulfonate users, which resulted in 10,311 unique drug-polystyrene sulfonate combinations.

We selected the 100 most frequently co-dispensed drugs with sevelamer and with polystyrene sulfonate. For these 100 drugs, 14,739 unique drug-sevelamer combinations and 7,123 unique drug-polystyrene sulfonate combinations were extracted from the database, which covered about 70% of the total unique drug-sevelamer/polystyrene sulfonate combinations.

Table 2 shows the categorization of these 100 drugs in ATC-class first level.

Table 2
One hundred most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate, by ATC-class first level

Drug category (ATC-first level)	Sevelamer (N*, (%)) Ntotal = 14,739	Polystyrene sulfonate (N*, (%)) Ntotal = 7,123
A. Alimentary tract and metabolism	3,597 (24.4)	1,660 (23.3)
B. Blood and blood forming organs	1,806 (12.3)	1,026 (14.4)
C. Cardiovascular system	3,231 (21.9)	2,074 (29.1)
D. Dermatologicals	958 (6.5)	416 (5.8)
G. Genito-urinary system and sex hormones	50 (0.3)	34 (0.5)
H. Systemic hormonal preparations, excluding sex hormones and insulines	541 (3.7)	259 (3.6)
J. Antiinfectives for systemic use	1,378 (9.3)	579 (8.1)
L. Antineoplastic and immunomodulating agents	66 (0.4)	72 (1.0)
M. Musculo-skeletal system	374 (2.5)	207 (2.9)
N. Nervous system	1,408 (9.6)	455 (6.4)
R. Respiratory system	474 (3.2)	156 (2.2)
S. Sensory organs	293 (2.0)	120 (1.7)
V. Various	563 (3.8)	65 (0.9)
* number of unique drug-sevelamer/polystyrene sulfonate combinations		

In sevelamer users, 58.6% of the co-dispensed drugs were from ATC-classes A, B and C and in polystyrene sulfonate users this was 66.8%. These included proton pump inhibitors, laxatives, vitamin D analoga, antidiabetic agents as insulins, drugs for treating renal anaemia, antiplatelet coagulation drugs, antithrombotics, antihypertensive drugs, heart failure treatment and lipid lowering treatment. Other frequently co-dispensed drugs were dermatologicals (indifferent dermatological products, dermal corticosteroids,anti-infective treatment), ATC class H (prednisolon, cincacalcet, levothyroxine) ATC class L (mycophenolic acid, tacrolimus), ATC class M (allopurinol, colchicine), and ATC-class N (pain medication, benzodiazepines). The individual top 10 drugs co-dispensed with sevelamer (with the percentage of patients who received the combination during the study period) were alfacalcidol (59.4%), metoprolol (50.0%), omeprazole (43.5%), calcium carbonate (39.6%), furosemide (38.9%), acetylsalicylic acid (36.3%), amlodipine (33.1%), macrogol (31.5%), ferrofumarate (28.3%) and prednisolone (26.8%). For polystyrene sulfonate the individual top 10 included alfacalcidol (45.4%), metoprolol (43.4%), omeprazole (35.5%), furosemide (32.5%), amlodipine (30.7%), calcium carbonate (29.6%), ferrofumarate (27.9%), acetylsalicylic acid (26.3%), simvastatin (24.4%) and prednisolone (22.9%).

After application of the described exclusion criteria, a list of 39 drugs co-dispensed with sevelamer and 47 drugs co-dispensed with polystyrene sulfonate was compiled for further exploration of interaction potential (Fig. 2). Table 3 presents the selected drugs, the number of unique drug-sevelamer/polystyrene sulfonate combinations, the percentage of sevelamer/polystyrene sulfonate users having received these drugs and the results of the analysis of potential new binding interactions based on pKa- and Log P values. We identified 22 and 27 potentially clinically relevant new binding interactions for sevelamer and polystyrene sulfonate, respectively.

Table 3
Most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate and assessment of potential binding interactions

	Sevelamer (N = 1,083)					Polystyrene sulfonate			
Drug	pKa (acid) [31]	Log P [31]	Unique drug combination (N)	Patients (%)	Potential new binding interaction (Yes/No)	Drug	pKa (base) [31]	Unique drug combination (N)	Patien (%)
Calcium carbonate	6.1	0.3	429	39.6	No[a]	Alfacalcidol	-2.8	325	45.4
Acetylsalicylic acid	3.4	1.2	393	36.3	Yes	Metoprolol	9.7	311	43.4
Amlodipine	19.1	1.6	358	33.0	No	Omeprazol	4.8	254	35.5
Macrogol	-	-	341	31.5	No	Furosemide	-1.5	233	32.5
Ferrofumarate	3.4	< 0	307	28.3	No[a]	Amlodipine	9.5	220	30.7
Prednisolone	12.6	1.27	290	26.8	No	Calcium carbonate	-	212	29.6
Amoxicillin/clavulanic acid	3.2/3.3	< 0	285	26.3	Yes / Yes	Ferrofumarate	-	200	27.9
Acenocoumarol	5.8	2.7	272	25.1	Yes	Acetylsalicylic acid	-7.1	188	26.3
Lanthanum carbonate	6.1	0.3	259	23.9	No[a]	Prednisolone	-2.9	164	22.9
Polystyrene sulfonate	-	-	245	22.6	No	Macrogol	-	157	21.9
Acetaminophen	9.5	0.9	214	19.8	No	Acenocoumarol	-6.8	149	20.8
Lactulose	10.3	< 0	213	19.7	No	Enalapril	5.2	138	19.3
Tramadol	13.8	2.5	212	19.6	Yes	Pantoprazol	3.6	121	16.9
Cinacalcet	-	6.3	184	17.0	Yes	Amoxicillin/clavulanic acid	7.4/ -2.6	111	15.5
Bumetanide	4.7	2.4	165	15.2	Yes	Acetaminophen	-4.4	102	14.2
Doxycycline	3.3	< 0	156	14.4	Yes	Ciprofloxacin	8.7	95	13.3
Doxazosin	12.7	2.1	145	13.4	Yes	Allopurinol	1.3	88	12.3
Flucloxacillin	3.8	2.4	125	11.5	Yes	Bumetanide	2.7	86	12.0
Allopurinol	8.5	0	125	11.5	No	Doxazosin	7.2	84	11.7
Metoclopramide	14.5	1.4	121	11.2	No	Colecalciferol	-1.3	81	11.3
Oxazepam	10.6	2.9	121	11.2	Yes	Lactulose	-3.0	78	10.9
Codeine	13.8	1.3	121	11.2	No	Bisoprolol	9.7	75	10.5
Oxycodone	13.6	1.0	120	11.1	No	Tramadol	9.2	74	10.3
Nifedipine	-	1.8	116	10.7	No	Isosorbide mononitrate	-3.5	72	10.0
Colchicine	15.1	1.5	116	10.7	No	Colchicine	0	70	9.8
Bisoprolol	14.1	2.2	112	10.3	Yes	Doxycyclin	8.3	69	9.6
Isosorbide mononitrate	13.3	< 0	105	9.7	No	Hydrochlorothiazide	-2.7	69	9.6
Lisinopril	3.2	< 0	103	9.5	Yes	Lanthanum carbonate	-	65	9.1
Clopidogrel	-	4.0	101	9.3	Yes	Nifedipine	5.3	65	9.1
Clindamycin	12.4	1.0	97	9.0	No	Lisinopril	10.2	64	8.9
Amitriptyline	-	4.8	88	8.1	Yes	Oxazepam	-1.5	62	8.7
Sulfamethoxazol/trimethoprim	6.2/17.3	0.8/1.3	88	8.1	Yes / No	Oxycodone	8.8	58	8.1

[a] Sevelamer may bind carbonate or fumarate but not the clinically effective ions calcium, iron and lanthanum

[b] Although theoretically polystyrene sulfonate could bind the positively charged calcium, this would not lead to a binding interaction in clinical practice, consi availability of a polystyrene sulfonate product as a calcium-salt

[c] Polystyrene sulfonate may bind the positively charged iron and lanthanum ions

	Sevelamer (N = 1,083)						Polystyrene sulfonate		
Losartan	7.4	5.1	85	7.8	Yes	Flucloxacillin	-0.9	52	7.3
Diclofenac	4.0	4.3	84	7.8	Yes	Irbesartan	4.1	52	7.3
Irbesartan	7.4	5.5	81	7.5	Yes	Spironolactone	-4.9	50	7.0
Hydrochlorothiazide	9.1	< 0	71	6.6	No	Diclofenac	-2.1	49	6.8
Loperamide	14.0	4.8	71	6.6	Yes	Clopidogrel	5.1	48	6.7
Vitamin B complex/vitamin C	15.5/4.4	< 0 /< 0	64	5.9	No / Yes	Cinacalcet	10.3	48	6.7
Bisacodyl	-	3.6	55	5.1	Yes	Perindopril	5.5	48	6.7
						Mycophenolic acid	-4.1	46	6.4
						Codeine	9.2	44	6.1
						Amitriptyline	9.8	43	6.0
						Gliclazide	1.4	43	6.0
						Esomeprazole	4.8	43	6.0
						Losartan	4.1	37	5.2
						Dipyridamole	6.6	36	5.0
						Metformin	12.3	36	5.0
[a] Sevelamer may bind carbonate or fumarate but not the clinically effective ions calcium, iron and lanthanum									
[b] Although theoretically polystyrene sulfonate could bind the positively charged calcium, this would not lead to a binding interaction in clinical practice, consi availability of a polystyrene sulfonate product as a calcium-salt									
[c] Polystyrene sulfonate may bind the positively charged iron and lanthanum ions									

Discussion

This study identified several novel potential binding interactions for sevelamer and polystyrene sulfonate using an *in silico* approach.

The 100 most frequently co-dispensed drugs with sevelamer or polystyrene sulfonate found in this study are in line with other drug utilization studies done in patients with CKD and haemodialysis patients [2–7, 9]. Cardiovascular drugs, antidiabetic agents, drugs for the treatment of metabolic disorders, proton pump inhibitors, laxatives, anaemia-, anticoagulation-, gout treatment, anti-infectives, dermatological products and pain medication were the main drug categories reported in those studies [2–7, 9]. This confirms the suitability of the IADB database for this research [27].

The high number of unique drug-sevelamer/polystyrene sulfonate combinations found in this study can be explained by polypharmacy of this population, switching of drugs because of inefficacy or adverse effects, prescription of drugs for short duration, for example antibiotics and the long study period of 19 years.

In several studies the prevalence of drug-drug interactions in CKD patients is reported to be high, i.e. 75–91%, and is associated with the number of prescribed drugs, age, the stage of CKD, as well as comorbidities as diabetes mellitus, hypertension and obesity [5–9]. However, these studies did not report binding interactions among the top 10 drug-drug interactions, despite the fact that several binding interactions with sevelamer and polystyrene sulfonate are already known and both drugs are widely used by patients with CKD stage 4 or 5 [10,11,16–25,31]. The lack of reporting of binding interactions may be because previous studies included patients with all stages of CKD instead of only patients with CKD stage 4 and 5. In addition, different (software) methods for identifying drug-drug interactions are used in these studies. Furthermore, the study of Sommer et al. focused on pharmacodynamic interactions instead of pharmacokinetic interactions [8].

We identified 22 and 27 potentially relevant binding interaction candidates for sevelamer and polystyrene sulfonate respectively for further interaction research. We suggest performing *in vitro* experiments for those drugs to gather knowledge on clinically relevant binding interactions by simulating gastro-intestinal conditions in the laboratory in the presence and absence of sevelamer or polystyrene sulfonate. Walker et al. showed that *in vitro* binding studies using colesevelam are very sensitive but have a low specificity for identifying compounds binding to the drug [34]. No binding *in vitro* meant that the likelihood

for binding *in vivo* was very small. On the other hand, when there is binding *in vitro* this will not automatically imply there is binding *in vivo*. This is because drug absorption from the gastro-intestinal tract is affected by many different factors as absorptive surface area, pH, food effects, intestinal transit time, passive intestinal permeability, intestinal transporters and enzymes, which are not all accounted for in *in vitro* experiments [35]. So confirmatory *in vivo* studies are necessary to assess the clinical relevance of *in vitro* binding findings. *In vitro* screening is however, a valuable tool to test a large number of drugs, to limit the number of candidates for subsequent clinical drug interaction studies.

Strengths of this study are extracting the most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate from a large, up-to-date and representative database and analysing these for their interaction potential based on pKa and Log P values. The analysed top 100 co-dispensed drugs covered about 70% of the unique drug-sevelamer/polystyrene sulfonate combinations. However, we considered combinations received by less than 5% of the sevelamer/polystyrene sulfonate users as clinically less relevant to assess for potential interaction potential and the analysed top 100 covered all drugs used by more than 5% of the sevelamer/polystyrene users.

The interaction potential was assessed based on a minimum of 50% negatively or positively charged availability of the drugs at gastrointestinal pH levels based on pKa-values. For sevelamer also lipophilicity was assessed by taking into account Log P values. Computational approaches have also been developed to identify novel drug-drug interactions in silico [36]. Which approach is most successful in determining clinically relevant drug-drug interactions has not been determined yet. A limitation of our study is that prescribing in this patient group may be different in other regions of the world or in other health care systems, so we may have missed clinically relevant drugs with potential to interact, which are infrequently prescribed in the Netherlands.

Conclusion

In conclusion, we identified several candidates for potential novel binding interactions with sevelamer and polystyrene sulfonate from data on co-dispensed drugs and through an assessment of the chemical properties of these drugs. Further *in vitro* studies should be performed with those candidates.

Declarations

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Conflicts of interest

All authors have no conflicts of interest to declare.

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Supplementary Data

Drugs excluded from the top 100 co-dispensed drugs for which there is evidence for an interaction or evidence that there is no interaction based on literature were excluded [10-24].

Sevelamer

Interaction: Levothyroxine, Ciprofloxacin, Mycophenolic acid, Vitamin D analoga, Folic acid, Furosemide, Proton pump inhibitors

No interaction: Metoprolol, Enalapril, Digoxine

Polystyrene sulfonate

Interaction: Levothyroxine

Figures

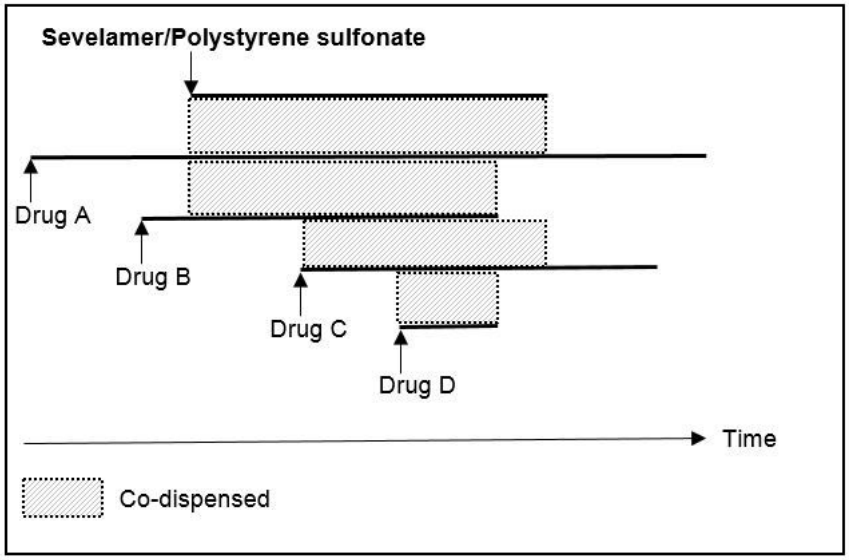

Figure 1

Graphic presentation of the identification of drugs A, B, C and D which were co-dispensed with sevelamer or polystyrene sulfonate

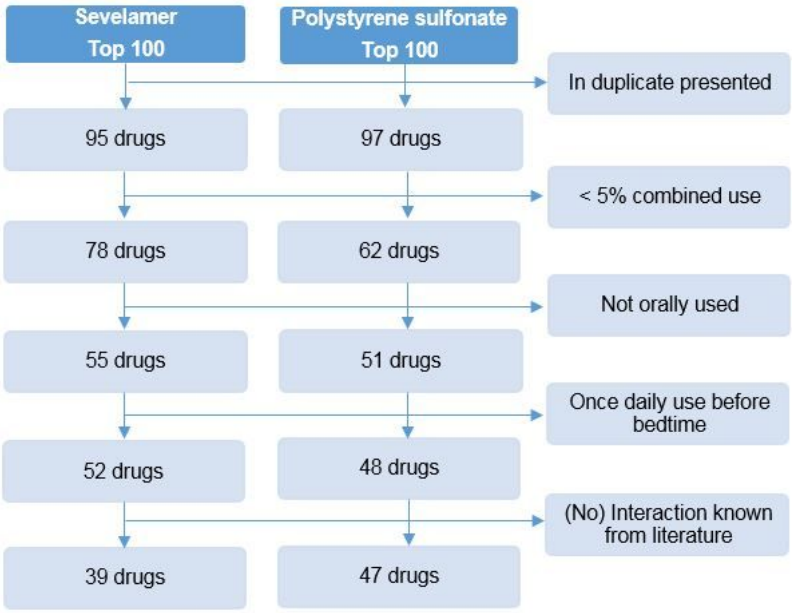

Figure 2

Selection of co-dispensed drugs with sevelamer or polystyrene sulfonate for further interaction research