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Impact of phosphate binders on quality of life in dialysis patients: Results from the prospective Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes study

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Abstract

Background: Phosphate binders cause high pill burden for dialysis patients, complicate medication regimens, and have unpleasant taste and large size which may affect patients' quality of life. This study explores the association between phosphate binder pill burden and health-related quality of life (HRQoL) in dialysis patients.

Methods: We conducted a cross-sectional multi-centre cohort study in 21 Dutch dialysis centres. Phosphate binder pill burden was extracted from electronic patient records. Primary outcome was HRQoL measured with the Short Form 12 physical and mental component summary scores (PCS and MCS). Secondary endpoints were severity of gastro-intestinal symptoms, itching, dry mouth, and mental health symptoms, measured with the Dialysis Symptom Index.

Results: Of 388 included patients, aged 62 ± 16 years, 77% underwent haemodialysis. PCS scores were comparable for patients with and without phosphate binders. Patients using 1–3 pills reported lower scores for decreased appetite (β −0.5; 95%CI −0.9 to −0.2), implying better appetite, than patients without phosphate binders. Patients using 4–6 pills also reported lower scores for decreased appetite (β −0.5; 95%CI −0.8 to −0.1) and for itching (β −0.5; 95%CI −0.9 to −0.1). Patients using >6 pills reported lower MCS (β −2.9; 95%CI −6.2–0.4) and higher scores for feeling nervous (β 0.6; 95%CI 0.1–1.1) and feeling sad (β 0.4; 95%CI 0.0–0.9).

Conclusion: Phosphate binder pill burden is not associated with physical quality of life. A higher pill burden is associated with better appetite and less itching. Patients using >6 pills per day report lower mental quality of life and felt nervous and sad more often.

KEYWORDS
dialysis, phosphate binders, phosphate binding agents, polypharmacy, quality of life

Summary at a glance

This cross-sectional cohort study assessed the impact of phosphate binders on quality of life in dialysis patients. A higher phosphate binder pill burden was associated with worse mental quality of life, more severe feelings of nervousness and sadness, a better appetite, and less severe feelings of itching but not with physical quality of life.

1 | INTRODUCTION

Dialysis patients are prescribed many medications to improve metabolic control and manage comorbidities. They are prescribed on average 9–12 types of medications and have a daily pill burden of 15–19 pills.[1–3] A recent study found that a larger number of medications is associated with a lower health-related quality of life (HRQoL) and a higher number of symptoms in dialysis patients.[3]

The group of medications contributing most to dialysis patients' pill burden are phosphate binders which comprise 30%–50% of their pill burden.[1,2] These drugs are typically prescribed to manage hyperphosphatemia, one of the typical sequelae of chronic kidney disease and an important risk factor for cardiovascular disease and mortality.[4,5]

Besides their high pill burden, phosphate binders, complicate medication regimens.[6] Patients have to strictly adhere to specific intake instructions in order for phosphate binders to exert optimal serum phosphorus-reducing effects. They must be taken during meals (i.e., usually thrice daily) with a possible additional dose when consuming certain snacks in-between meals. Additionally, patients can find the pills hard to swallow due to their large size and some patients find their taste unpleasant. As a result, patients may feel aversion towards phosphate binders. It is therefore not surprising that adherence to these medications is notably poor with a reported rate of non-adherence as high as 93%.[7,8]

To our knowledge, no study has studied the impact of phosphate binders on dialysis patients' HRQoL, despite the numerous inconveniences and discomforts of these medications affecting patients' daily lives. Therefore, the primary aim of this study is to gain insight in the association between phosphate binder pill burden and HRQoL in dialysis patients. Our secondary aim is to explore the association between the phosphate binder pill burden and gastro-intestinal symptoms, itching, dry mouth, and mental-health related symptoms. We hypothesize that patients with a higher pill burden of phosphate binders experience a lower HRQoL and more symptoms.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

The methods and reporting of this study adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[9] This study is part of the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO).[10] DOMESTICO is a prospective observational cohort study in Dutch and Belgian dialysis centres that compares the HRQoL and clinical outcomes of patients undergoing home and in-centre dialysis and the cost-effectiveness of these therapies. Data are collected at the start of dialysis, at 3, 6, and every 6 months thereafter. Patients are eligible to participate if they are 18 years or older and have end-stage kidney failure for which they require to start with haemodialysis or peritoneal dialysis. Exclusion criteria are current treatment with maintenance dialysis, expectation to receive a kidney transplant within 3 months, or a life expectancy shorter than 3 months. The Amsterdam University Medical Centre Medical Ethics Review Board approved the study protocol (NL63277.029.17). All patients provided written informed consent.

For this study, we selected a cross-sectional sample of the DOMESTICO cohort 3 months after dialysis initiation. This visit was selected since the start of dialysis can be a turbulent period for patients which might temporarily affect their HRQoL and because phosphate binder prescription needs to be adapted to the additional phosphorus clearance through dialysis. We estimated that at 3 months patients have had the time to get used to a life with dialysis and their nephrologist has updated their phosphate binder prescription to account for phosphate clearance through dialysis Another consideration was the fact that the 3 month visit was the moment at which the most data were available, maximizing the available statistical power. The sample consisted of patients from 21 Dutch dialysis centres: 5 academic hospitals, 14 community hospitals, and 2 stand-alone dialysis centres. Centres were included if we could retrieve data on phosphate binder use. Patients were screened for inclusion up to

March 2021. Additional exclusion criteria applicable to this study were a missing medication list and a missing or incomplete (i.e., filled for <75%) Short Form 12 (SF-12) which was the primary questionnaire to measure HRQoL.

2.2 | Phosphate binder use

The prescription and pill burden of phosphate binders was collected from patients' electronic patient records. The following phosphate binders were included: calcium carbonate (World Health Organization Anatomical Therapeutic Chemical [ATC] code A12AA04), sevelamer (ATC V03AE02), lanthanum carbonate (ATC V03AE03), calcium acetate/magnesium carbonate (ATC V03AE04), and sucroferric oxyhydroxide (ATC V03AE05). The prescribed phosphate binding equivalent dose was converted to grams of calcium carbonate.[11,12]

2.3 | Health-related quality of life

The primary outcomes for HRQoL were the Physical Component Summary (PCS) Score and Mental Component Summary (MCS) Score measured with the SF-12.[13] This generic quality of life questionnaire comprises 12 questions from the Short Form 36 and has been validated for dialysis patients.[14–17] Scores range from 0 to 100 and were standardized to United States population scores with a mean of 50 and a standard deviation (SD) of 10. A difference of three points in PCS or MCS was considered clinically significant.[18] In addition, patients rated their own health on the visual analogue scale of the EuroQoL-5D-5L.[19] Higher scores indicate a better quality of life for both the SF-12 and patients' self-rated health. Patients filled out questionnaires online or on paper. If a patient's 3-month questionnaire was missing, their 6-month questionnaire was used instead.

2.4 | Symptoms

Presence and severity of symptoms were measured with the Dialysis Symptom Index (DSI) which has been validated for the routine measurement of symptoms in dialysis patients.[20,21] Patients fill out 2 items for 30 different symptoms. On the first item they indicate whether or not they experience a particular symptom and on the second its severity on a 5-point Likert scale ranging from 'not at all burdensome' to 'very burdensome'. For this study, these two items were aggregated into a 6-point Likert scale score ranging from 0 ('did not experience symptom') to 5 ('symptom is very burdensome'). We specifically focussed on gastro-intestinal symptoms as they are described as typical side effects of phosphate binders in consumer medicine information leaflets.[22–24] Additionally, we investigated mental health-related symptoms because we hypothesised that the main burden from phosphate binders comes from their complex intake schedule, high pill burden, and unpleasant taste and size rather than physical discomforts.[6] We also looked at the symptom dry mouth because phosphate binders sometimes are prescribed in the form of chewing pills and at itching because some studies suggest that hyperphosphatemia, which phosphate binders abate, is associated with this symptom.[25,26] The included symptoms are listed in Table 1.

TABLE 1 Included symptoms selected from the Dialysis Symptom Index[a]

Gastro-intestinal symptoms
1. Constipation
2. Nausea
3. Vomiting
4. Diarrhoea
5. Decreased appetite
Mental health-related symptoms
6. Difficulty concentrating
7. Worrying
8. Feeling nervous
9. Feeling irritable
10. Feeling sad
11. Feeling anxious
Miscellaneous symptoms
12. Itching
13. Dry mouth

[a]The full Dialysis Symptom Index comprises 30 symptoms.[19]

2.5 | Other variables

Patient demographic factors, medical history, dialysis treatment, and laboratory parameters were collected from patients' electronic patient files or the Dutch Renal Registry (RENINE). Level of comorbidity was quantified with the Charlson Comorbidity Index which includes a range of chronic conditions.[27] Residual kidney function, as proxy for phosphate excretion, was estimated from serum creatinine and 24-hour urine creatinine levels. Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (metres).

2.6 | Statistical methods

Continuous variables are described as mean ± SD or median (interquartile range [IQR]). Categorical variables are presented as frequencies (percentages). Patients were divided into categories of using 0 pills, 1–3 pills, 4–6 pills, and >6 pills of phosphate binders due to violation of linearity assumptions. The characteristics of patients in different groups were compared using Chi square tests, analysis of variance (ANOVA), or Kruskal–Wallis tests. Data were analysed using linear regression. We adjusted for confounding using three models of increasing complexity: model 1 was adjusted for demographic factors and comorbidity (age, sex, and Charlson Comorbidity Index), model

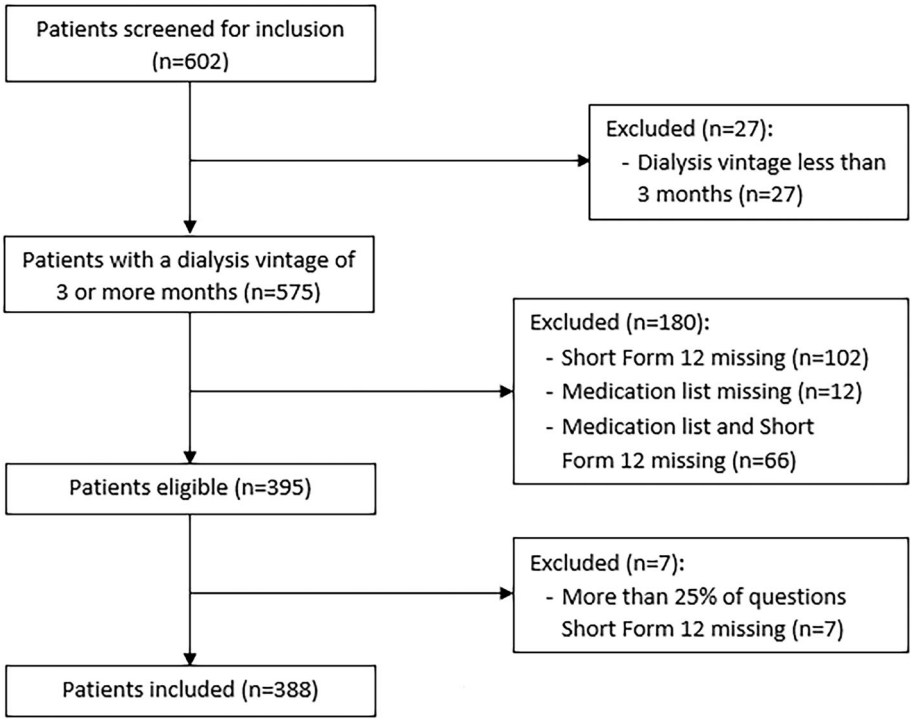

FIGURE 1 Flow chart of participant selection

2 contained the variables of model 1 and BMI and protein catabolic rate as a proxy for phosphate intake, and model 3 contained the variables of model 2 and serum phosphorus levels and residual kidney function.

Multiple imputation techniques were used to create 40 datasets. Missing covariates were imputed using predictive mean matching. The proportion of missing data was less than 5% for all covariates except for protein catabolic rate (42%), cause of kidney disease (35%), BMI (10%), and residual kidney function (8%). The response rate for questionnaires was high: for the SF-12, only 38 patients (10%) missed one or more items and for the DSI symptom scores less than 5% of patients missed any of the symptoms. We imputed single questions for the SF-12 for patients with less than 25% of missing items from which we calculated SF-12 summary scores. Characteristics of patients with and without missing data were compared using t tests and Chi square tests. No significant differences were observed between patients with and without missing data.

Statistical analyses were performed in Stata Statistical Software (version 15.1 StataCorp LLC, College Station, TX, United States). Mean differences in PCS, MCS, symptom score, self-rated health and 95% confidence intervals (95%CI) were reported. *p* Values were considered statistically significant if <.05.

3 | RESULTS

3.1 | Patient selection and characteristics

In total, 602 patients were screened of whom 395 met the inclusion criteria. After excluding participants with too many missing SF-12 items, 388 patients were enrolled. Main reasons for exclusion were a current dialysis vintage of less than 3 months ($n = 27$), missing SF-12 ($n = 102$) and a combination of missing SF-12 and missing medication list ($n = 66$) (Figure 1). Excluded patients had a higher Charlson Comorbidity Score, and serum phosphorus levels.

Characteristics of included patients are outlined in Table 2. Mean age was 62 ± 16 years, 128 (33%) were female, and 293 (77%) underwent haemodialysis. Of included patients, 294 (77%) were prescribed phosphate binders with a median pill burden of 4 (IQR 3–7) and a maximum of 16 pills a day. Of patients who were prescribed phosphate binders, 221 (75%) received one type of phosphate binder, 69 (24%) two types, and 4 (1%) three types of phosphate binders. The combinations of prescribed phosphate binders are illustrated in Figure 2. The most frequently prescribed phosphate binder was sevelamer, followed by lanthanum carbonate, and calcium carbonate (respectively 70%, 31%, and 20% of patients with phosphate binders). Almost no patients were prescribed calcium acetate/magnesium carbonate or sucroferric oxyhydroxide (4% and 1% of patients with phosphate binders, respectively). Patients with a higher pill burden were more often male, younger, and had a lower residual kidney function and higher serum phosphorus.

3.2 | Association between phosphate binder pill burden and health-related quality of life

Patients reported a mean PCS of 37.0 ± 10.0, mean MCS of 47.4 ± 10.1, and mean self-rated health of 62 ± 20 (Table 2). For 56 patients (14%) their 6-month questionnaire was used because their 3-month questionnaire was missing. Crude reported PCS and self-

TABLE 2 Characteristics of participants by phosphate binder pill burden

	All patients ($n = 388$)	0 pill ($n = 94$)	1–3 pill ($n = 112$)	4–6 pill ($n = 101$)	>6 pill ($n = 81$)
Demographics					
Age (years)	62 ± 16	66 ± 15	63 ± 16	63 ± 15	56 ± 17
Female sex	128 (33)	41 (44)	38 (34)	25 (25)	24 (30)
Medical and kidney history					
Cause of kidney failure[a]					
Glomerulonephritis/sclerosis	26 (10)	7 (12)	6 (8)	7 (10)	6 (12)
Cystic kidney disease	15 (6)	3 (5)	8 (11)	1 (1)	3 (6)
Hypertension/renovascular	62 (24)	17 (28)	18 (24)	17 (25)	10 (19)
Diabetes mellitus	56 (22)	13 (21)	11 (15)	19 (28)	13 (25)
Miscellaneous	45 (18)	9 (15)	14 (19)	13 (19)	9 (17)
Unknown	50 (20)	12 (20)	17 (23)	10 (15)	11 (21)
Charlson comorbidity index	3 [2–5]	4 [2–5]	3 [2–4.5]	3 [2–5]	3 [2–5]
Previously underwent dialysis	92 (24)	30 (32)	26 (23)	19 (19)	17 (21)
Dialysis modality[a]					
Haemodialysis	293 (77)	67 (74)	82 (74)	83 (83)	61 (75)
Peritoneal dialysis	89 (23)	24 (26)	29 (26)	17 (17)	19 (24)
Residual diuresis (>100 ml/day)	324 (89)	80 (88)	92 (91)	85 (91)	67 (86)
Residual GFR (ml/min/1.73 m^2)[b]	7 ± 5	9 ± 6	8 ± 5	7 ± 4	6 ± 3
BMI (kg/m^2)	27.1 ± 5.7	26.9 ± 5.9	26.7 ± 5.8	27.7 ± 5.2	27.2 ± 5.9
PCR (g/kg/day)	0.99 ± 0.32	0.98 ± 0.36	0.96 ± 0.33	1.02 ± 0.30	1.00 ± 0.31
Laboratory					
Phosphorus (mmol/L)	1.68 ± 0.47	1.50 ± 0.38	1.62 ± 0.38	1.74 ± 0.51	1.90 ± 0.54
Calcium (mmol/L)	2.26 ± 0.21	2.25 ± 0.15	2.22 ± 0.24	2.29 ± 0.13	2.29 ± 0.27
PTH (mmol/L)	24.8 [13.6–45.2]	22.0 [12.0–41.5]	26.0 [14.7–44.0]	28.6 [12.8–49.0]	26.0 [16.0–49.5]
Albumin (g/L)	37 ± 6	36 ± 5	36 ± 6	37 ± 7	37 ± 5
Phosphate binding agents					
Calcium carbonate	58 (15)	0 (0)	21 (19)	13 (13)	24 (30)
Sevelamer	206 (53)	0 (0)	60 (54)	71 (70)	75 (93)
Lanthanum carbonate	90 (23)	0 (0)	31 (28)	34 (34)	25 (31)
Calcium acetate/magnesium carbonate	13 (3)	0 (0)	3 (3)	5 (5)	5 (6)
Sucroferric oxyhydroxide	4 (1)	0 (0)	2 (2)	1 (1)	1 (1)
Number of phosphate binders	1.0 ± 0.7	0 ± 0	1.0 ± 0.2	1.2 ± 0.4	1.6 ± 0.6
Phosphate binding equivalent dose	2.7 [0.5–4.8]	0.0 [0.0–0.0]	1.8 [1.4–3]	3.6 [3.0–6.0]	5.4 [5.4–7.8]

TABLE 2 (Continued)

	All patients ($n = 388$)	0 pill ($n = 94$)	1–3 pill ($n = 112$)	4–6 pill ($n = 101$)	>6 pill ($n = 81$)
Health-related quality of life					
Short Form 12					
PCS score	37.0 ± 10.0	35.6 ± 9.9	37.6 ± 10.1	38.0 ± 9.9	36.4 ± 10.2
MCS score	47.4 ± 10.1	48.2 ± 10.7	48.5 ± 9.4	47.5 ± 9.6	44.7 ± 10.8
EuroQoL 5D-5L					
Self-rated health	62 ± 20	60 ± 20	64 ± 21	64 ± 18	59 ± 21

Note: Continuous variables are described as mean ± SD or median (interquartile range). Categorical variables are described as *n* (%).

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; MCS, Mental Component Summary; PCR, protein catabolic rate; PCS, Physical Component Summary; PTH, parathyroid hormone.

[a]For categorical variables, only patients without missing value are included. Therefore, the sum of patients may not equal the total number of patients.

[b]Only for patients with residual kidney function ($n = 324$).

rated health score were comparable across the four categories of phosphate binder pill burden. We observed a trend towards lower MCS scores for patients with a pill burden of >6 pills ($p = .08$) (Table 2).

The results of the analyses for the association between phosphate binder pill burden and HRQoL are detailed in Table 3 and Figure 3. No association was observed between phosphate binder pill burden and PCS and patients' self-rated health in neither the crude nor the adjusted analyses. There was also no association between phosphate binder pill burden and MCS for patients with a pill burden of 0, 1–3, and 4–6 pills. However, patients with >6 pills reported a lower MCS score compared to patients without phosphate binders in the crude analyses (β −3.3; 95%CI −6.3 to −0.3; $p = .03$). This difference persisted after adjusting for confounding in model 1 and 2 but diminished after correction for serum phosphorus and residual kidney function (adj. β −2.9; 95%CI −6.2–0.4; $p = .08$).

3.3 | Association between the phosphate binder pill burden and symptom scores

The prevalence of reported symptoms among patients was high. The most frequently reported symptoms were itching (52%), dry mouth (40%), and worrying (39%). An overview of the prevalence and intensity of symptoms is visualized in Figure 4.

The results of the analysis for daily phosphate binder pill burden and symptom score are outlined in Table S1. Results of the crude and adjusted analyses were comparable. We did not find an association between gastro-intestinal symptoms and the amount of phosphate binders, except for decreased appetite: we observed a lower symptom score for decreased appetite (i.e., a better appetite) in patients with 1–3 and 4–6 pills (adj. β −0.5; 95% CI −0.9 to −0.2 and adj. β −0.5; 95% CI −0.8 to −0.1, respectively) compared to patients without phosphate binders in the fully adjusted analyses. For mental health-related symptoms, we observed higher symptom scores for feeling nervous and feeling sad for patients with >6 pills (adj. β 0.6; 95% CI 0.1–1.1 and adj. β 0.4; 95% CI 0.0–0.9, respectively) compared to patients without phosphate binders. Patients with 4–6 pills also reported lower symptom scores for itching compared to patients without phosphate binders (adj. β −0.5; 95% CI −0.9 to −0.1) but this was not found in patients using >6 pills.

4 | DISCUSSION AND CONCLUSIONS

To our knowledge, this is the first study to investigate the association between phosphate binder pill burden and HRQoL and symptom scores in dialysis patients. Phosphate binder pill burden was not associated with physical quality of life in dialysis patients nor with self-rated health on the visual analogue scale of the EuroQoL-5D-5L. No association between phosphate binder pill burden and mental quality of life was observed either for patients using 1–3 or 4–6 pills. Patients with >6 pills reported lower mental quality of life scores compared to

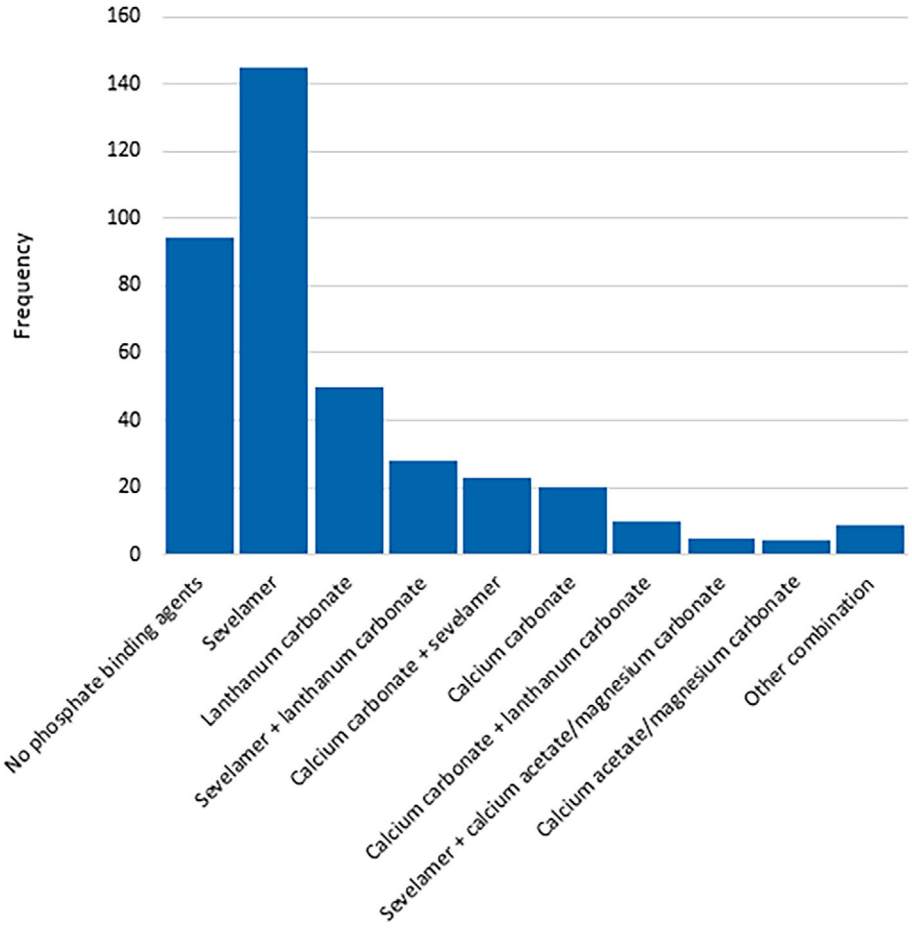

FIGURE 2 Overview of frequency of the prescription of different combinations of phosphate binding agents at 3 months after start of dialysis. Other combinations: sucroferric oxyhydroxide ($n = 2$), calcium carbonate + sevelamer + calcium acetate/magnesium carbonate ($n = 2$), calcium carbonate + calcium acetate/magnesium carbonate ($n = 1$), sevelamer + sucroferric oxyhydroxide ($n = 1$), lanthanum carbonate + calcium acetate/magnesium carbonate ($n = 1$), calcium carbonate + sevelamer + calcium acetate/magnesium carbonate ($n = 1$), and calcium carbonate + sevelamer + sucroferric oxyhydroxide ($n = 1$)

patients without phosphate binders. This difference of −2.9 is clinically relevant assuming a minimally important difference of three points.[18] Patients with >6 pills also reported higher scores for feeling nervous and feeling sad compared to patients without phosphate binders, corroborating our observation of lower MCS scores in these patients.

Contrary to medication information leaflets, we did not find an association with phosphate binder pill burden and gastro-intestinal symptoms apart from improved appetite for patients with 1–3 and 4–6 pills, compared to patients not using phosphate binders. Additionally, patients with 4–6 pills reported less severe itching. We hypothesize that these associations are not causal but may be explained by other factors or by coincidence. For instance, we hypothesize that lower scores for decreased appetite in patients with a higher pill burden might reflect a better health status. These patients are younger and have less comorbidity (Table 2), and therefore might have a better appetite resulting in a higher phosphorus intake.[28] This, in turn, would increase their need for phosphate binders to counteract a higher dietary phosphorus intake.

A causal relationship is conceivable for the observed association between phosphate binders and worse mental health in dialysis patients. Apart from their high pill burden, phosphate binders increase the complexity of medication regimens through their high number of intake moments and their pharmacological interactions with other medications.[8,29] Additionally, phosphate binders can interfere with patients' social lives because it is necessary to take these medications during meals. This means that patients must remember to bring their medication with them at all times if they are eating out. It becomes more difficult too for patients to conceal their medication use, if they wish, which may cause patients to encounter social stigmata and remind them of their illness.[8]

The impact of possible confounders on the results appeared limited. For example, after adjusting for age, sex, and comorbidity, the observed difference in PCS between patients with a pill burden of 1–3 and 4–6 pills somewhat decreased while this difference for patients with >6 pills reversed (Table 3, adjusted model 1), suggesting some confounding by these variables. Nevertheless, all point estimates remain far from statistically significant. Further adjusting for nutritional status (adjusted model 2) and, serum phosphorus, and residual kidney function (adjusted model 3) did not alter point estimations for PCS substantially. Estimations for the analysis with MCS remained stable in all three adjusted analyses despite an increase in p value indicating that none of the variables adjusted for caused significant confounding.

Phosphate binder use among Dutch dialysis patients 3 months after dialysis initiation was high. We observed significant practice variation in the prescription of (combinations) of phosphate binders considering that we registered 16 different combinations of phosphate

TABLE 3 Analysis of the association between phosphate binder pill burden and health-related quality of life

	Crude		Adjusted model 1[a]		Adjusted model 2[b]		Adjusted model 3[c]	
	Beta (95% CI)	*p* Value	Beta (95% CI)	*p* Value	Beta (95% CI)	*p* Value	Beta (95% CI)	*p* Value
Short-Form 12								
PCS								
0 pills	REF		REF		REF		REF	
1–3 pills	1.4 (−1.4–4.2)	.33	0.3 (−2.4–3.1)	.81	0.4 (−2.3–3.1)	.78	0.6 (−2.2–3.4)	.68
4–6 pills	1.7 (−1.2–4.5)	.25	0.3 (−2.5–3.1)	.84	0.2 (−2.6–3.0)	.87	0.6 (−2.4–3.6)	.70
>6 pills	0.3 (−2.7–3.3)	.86	−1.1 (−4.1–1.9)	.46	−1.1 (−4.2–1.8)	.44	−0.2 (−3.4–3.0)	.91
MCS								
0 pills	REF		REF		REF		REF	
1–3 pills	−0.3 (−3.1–2.4)	.82	−0.4 (−3.2–2.3)	.76	−0.5 (−3.2–2.3)	.75	−0.1 (−3.0–2.8)	.95
4–6 pills	−0.7 (−3.5–2.2)	.65	−0.8 (−3.7–2.0)	.57	−0.9 (−3.8–2.0)	.54	−1.0 (−4.1–2.0)	.51
>6 pills	−3.3 (−6.3 to −0.3)	.03[d]	−3.1 (−6.1–0.0)	.05	−3.1 (−6.2–0.0)	.05[d]	−2.9 (−6.2–0.4)	.08
EuroQoL 5D-5L								
Self-rated health								
0 pills	REF		REF		REF		REF	
1–3 pills	4.3 (−1.1–9.8)	.12	3.1 (−2.3–8.4)	.26	3.1 (−2.3–8.5)	.26	3.8 (−1.8–9.5)	.18
4–6 pills	4.1 (−1.5–9.7)	.15	2.5 (−3.1–8.0)	.38	2.3 (−3.3–7.9)	.42	3.1 (−2.9–9.0)	.31
>6 pills	−0.8 (−6.8–5.2)	.80	−1.3 (−7.3–4.7)	.67	−1.4 (−7.4–4.5)	.63	−0.3 (−6.8–6.1)	.92

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; MCS, Mental Component Summary; PCR, protein catabolic rate; PCS, Physical Component Summary.

[a]Adjusted for age, sex, and Charlson Comorbidity Index.

[b]Adjusted for age, sex, Charlson Comorbidity Index, body mass index (BMI), and protein catabolic rate (PCR).

[c]Adjusted for age, sex, Charlson Comorbidity Index, BMI, and PCR, serum phosphorus, and residual GFR.

[d]Statistically significant.

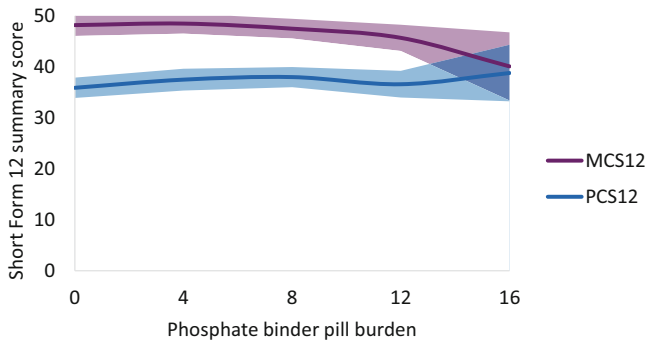

FIGURE 3 Association between phosphate binder pill burden and Physical and Mental Component Summary score

binders within this cohort (Figure 2). Despite the routine prescription of phosphate binders to dialysis patients, doubts remain which is the preferred strategy for the prescription of phosphate binders. The CKD-mineral and bone disorders guideline of the Kidney Disease: Improving Global Outcomes (KDIGO) provides little guidance on this topic.[30] Uncertainty exists to what extent phosphate binders help reduce cardiovascular morbidity and mortality in dialysis patients since placebo-controlled trials are lacking.[31,32] Three meta-analyses report lower mortality for sevelamer compared to calcium-based phosphate binders.[31–33] Observational data suggest that the prescription of phosphate binders as monotherapy or combination therapy is associated with lower all-cause and cardiovascular mortality.[34] In light of our findings and the ongoing debate about the efficacy of phosphate binders for dialysis patients, nephrologists may consider the high pill burden and impact on patients mental health before prescribing or increasing the dosage of phosphate binders and discuss these on an individual basis with their patients. Patient important outcome measures are a valuable tool to aid clinicians and patients in these discussions.[35]

This study has several limitations. First and foremost, the cross-sectional design prevents us from making causal inferences. In addition, we only used data 3 months after dialysis initiation. At this point most patients still have some residual kidney function to clear their serum phosphorus which diminishes their need for phosphate binders. As patients are treated for longer periods of time with dialysis, their residual kidney function generally declines, increasing the need for phosphate binders to manage serum phosphorus levels.[28] Therefore, the impact of phosphate binders on HRQoL might be more pronounced later in dialysis. Other limitations are that it is unclear whether patients themselves perceive that phosphate binders affect their quality of life and that we did not have information on patients' medication routines, the social impact of medications, and details on phosphate binder characteristics such as pill size and intake instructions

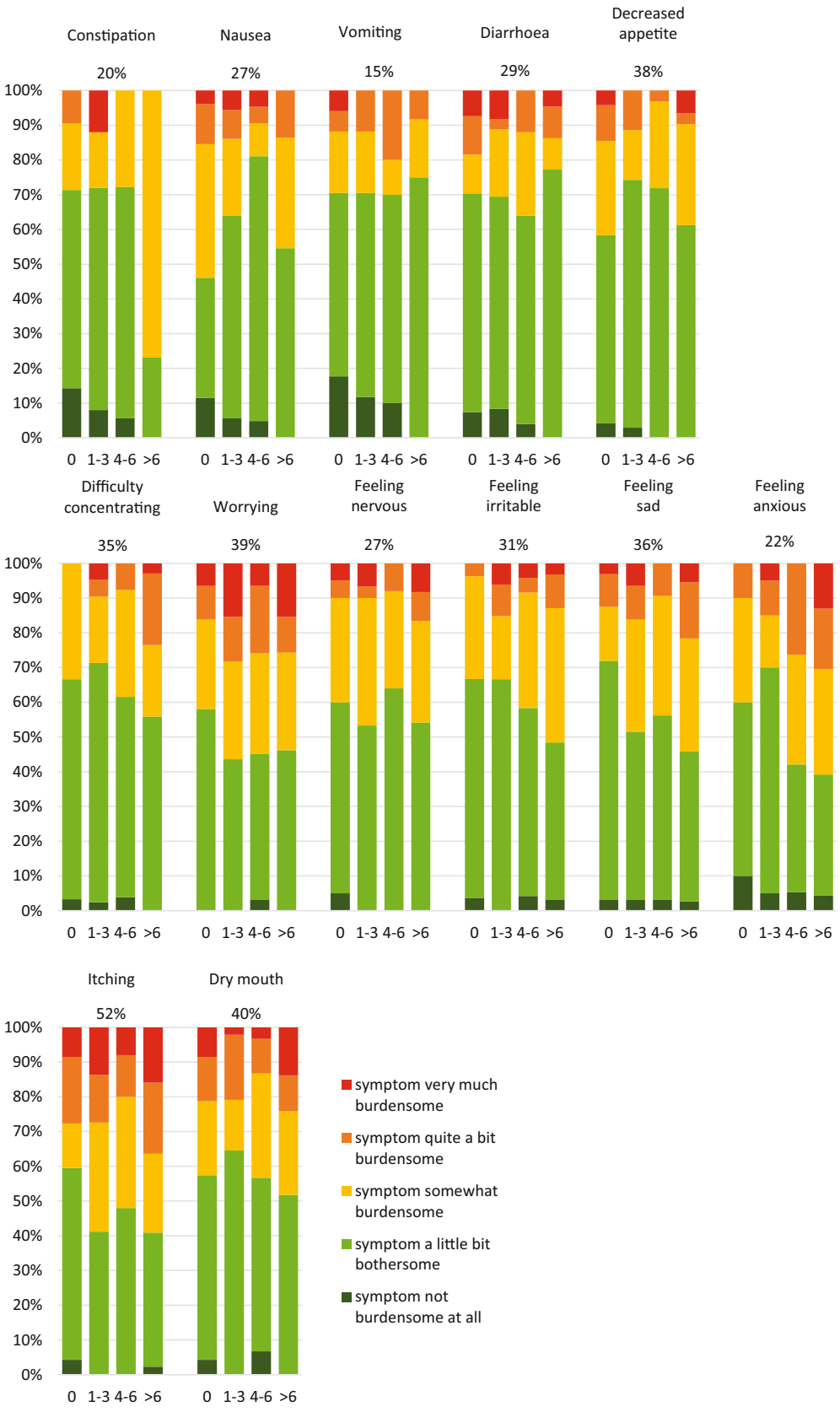

FIGURE 4 Prevalence and severity of gastro-intestinal and mental-health related symptoms, and itching, and dry mouth by phosphate binder pill burden at 3 months after the start of dialysis

(e.g., requirement to chew). These factors might be particularly relevant for phosphate binders since the intake of these medications is closely intertwined with patients' social lives. The clinical relevance of differences in symptom scores is also difficult to interpret because the clinimetric properties of our aggregated DSI scale have not been assessed. However, it is plausible that the

observed differences are clinically relevant considering the magnitude of the observed differences.

Strengths of this study are that the study population accurately reflects the Dutch dialysis population as we included patients from across the Netherlands from both academic and non-academic dialysis centres, the use of multiple validated questionnaires, and the high response rate for the questionnaires. Furthermore, we rigorously adjusted our results for possible confounders.

In conclusion, the results of this study suggest that a higher phosphate binder pill burden is associated with lower mental quality of life in dialysis patients but not with physical quality of life. Phosphate binder use is also associated with less severe symptoms of decreased appetite and itching and with more severe symptoms of feeling nervous and feeling sad. Further research should aim to provide further guidance on the place of phosphate binders in the treatment of dialysis patients, and corroborate our results in a longitudinal design. Additionally, a qualitative study should explore the perceived impact of medication on patients' daily lives.

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DATA AVAILABILITY STATEMENT

The data underlying this article are subject to an embargo of 12 months after completion of the DOMESTICO study. Once the embargo expires the data will be available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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