

Pill Burden, Adherence, Hyperphosphatemia, and Quality of Life in Maintenance Dialysis Patients

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Background and objectives: Dialysis patients have a high burden of co-existing diseases, poor health-related quality of life (HR-QOL), and are prescribed many medications. There are no data on daily pill burden and its relationship to HR-QOL and adherence to therapy.

Design, setting, participants, & measurements: Two hundred and thirty-three prevalent, chronic dialysis patients from three units in different geographic areas in the United States underwent a single, cross-sectional assessment of total daily pill burden and that from phosphate binders. HR-QOL, adherence to phosphate binders, and serum phosphorus levels were the three main outcome measures studied.

Results: The median daily pill burden was 19; in one-quarter of subjects, it exceeded 25 pills/d. Higher pill burden was independently associated with lower physical component summary scale scores on HR-QOL on both univariate and multivariate analyses. Phosphate binders accounted for about one-half of the daily pill burden; 62% of the participants were nonadherent. There was a modest relationship between pill burden from phosphate binders and adherence and serum phosphorus levels; these associations persisted on multivariate analyses. There was no relationship between adherence and serum phosphorus levels.

Conclusions: The daily pill burden in dialysis patients is one of the highest reported to date in any chronic disease state. Higher pill burden is associated with lower HR-QOL. There are many reasons for uncontrolled serum phosphorus levels; increasing the number of prescribed pills does not seem to improve control and may come at the cost of poorer HR-QOL.

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Patients undergoing maintenance dialysis have a high morbidity and mortality (1). Several studies have also shown that dialysis patients have a poor health-related quality of life (HR-QOL) and the HR-QOL is an independent predictor for death in these patients (2–6). The high burden of co-existing diseases, depression, and a high symptom burden explain, in part, the significant impairment in HR-QOL in dialysis patients (7,8). It has been reported that an average dialysis patient is expected to take 10 to 12 different types of medications (9,10). However, the authors are unaware of any study that has evaluated the daily pill burden and its relationship to HR-QOL. Furthermore, it is unclear if the relationship (if any) between pill burden and HR-QOL is independent of the burden of co-existing diseases.

The contribution of different classes of drugs to the daily pill burden in dialysis patients has also not heretofore been investigated. Clinical experience suggests that phosphate binders are probably the single largest contributor to the daily pill burden. Serum phosphorus has now consistently been shown to be an

independent predictor of the risk for death (11); the high pill burden from phosphate binders may affect patients' adherence to therapy and their ability to maintain optimal serum phosphorus levels (12). It is likely that the relationship between pill burden and hyperphosphatemia is bidirectional, and thus, a high pill burden may be one of the factors that limit ability to optimize serum phosphorus levels.

This cross-sectional study was undertaken to test the following hypotheses: phosphate binders are the largest contributors to the total daily pill burden of maintenance dialysis patients, and increasing pill burden is associated with impaired HR-QOL. The authors further posited that higher pill burden from phosphate binders is associated with lower adherence to therapy and higher serum phosphorus levels.

Materials and Methods

The study was conducted in dialysis units located in three different geographic areas in the United States: Torrance, CA (Harbor-UCLA, center 1); Denver, CO (University of Colorado, center 2); and Columbia, MO (University of Missouri-Columbia, center 3). The study was approved by the respective Institutional Review Boards. All patients undergoing maintenance dialysis for at least three months were approached for their interest in participation in the study. The study visit was scheduled at least seven days after the last prescription refill for one or more phosphate binder(s) that the subject had been prescribed.

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On the day of the study visit, subjects were asked to bring in all of the prescription and nonprescription medications they were currently taking. Demographic information was collected by subject interview, pill burden was documented after review of the medication containers and confirmed by subject interview, and HR-QOL was determined with a self-administered short-form 36 (SF-36) questionnaire (Quality Metric; Lincoln, RI) in either English or Spanish. Adherence to phosphate binders was determined by pill count.

The *total number of medications* was determined as the count of different oral medications the subject was taking at home and parenteral medications administered either at home (*viz.*, insulin) or in the dialysis unit. The *total pill burden* was defined as the total number of pills the subject took daily; for medications prescribed to be taken less frequently than daily or as per need, a fraction was assigned based on known or estimated frequency of usage, respectively. The *pill burden from phosphate binders* was defined as the total pill burden—with meals, snacks, or at bedtime—from any of the following medications: calcium carbonate, calcium acetate, sevelamer hydrochloride, lanthanum carbonate, and aluminum hydroxide. The pill burden from oral medications other than phosphate binders was assigned into categories modified from those used by the Dialysis Morbidity and Mortality Study, Wave 2 as: anti-hypertensives, other cardiovascular medications, vitamin D analogs/cinacalcet, gastrointestinal agents, endocrine/hormonal agents (including medications for diabetes, and dyslipidemia), psychotropic medications (like antidepressants), antithrombotic/antiplatelet agents, analgesics, and others (9). *Adherence with phosphate binder* was calculated as the ratio of the actual to the expected number of pills consumed from the time of last refill (obtained from prescription label) to the date of the study visit. The actual number of pills consumed was calculated as the difference between the number of pills dispensed and the pill count on the study date. The expected number of pills the subject should have consumed was calculated as the product of the daily pill burden from phosphate binders and the interval, in days, between the last refill and the study visit. In case of an interim hospitalization, the expected number of pills to be consumed was adjusted downward proportionate to the period of hospital admission. If a subject took more than one type of phosphate binder, the average of the adherence to the different medications was used for analysis. A subject was deemed to be adherent if he or she took 80% to 120% of the expected number of pills.

Co-morbidity and laboratory results were abstracted from clinical and electronic records. *Co-morbidity* was measured using Charlson's co-morbidity index through chart review. The results of the following *laboratory data*—serum levels of calcium, phosphorus, bicarbonate, parathyroid hormone, albumin, and Kt/V—were collected for the past three months, including the month of the study visit. The mean of all measured values over the three-month period was used for analysis. Bromocresol green was used to measure serum albumin at center 1 and bromocresol purple in centers 2 and 3. Serum parathyroid hormone (PTH) levels were measured using chemiluminescence enzymatic immunoassay (Bayer; Tarrytown, NY) at center 1, Beckman coulter immunoassay (Fullerton, CA) at center 2, and an enzyme immunoassay on an Immulite immunochemistry analyzer (Diagnostic Products, Los Angeles, CA) at center 3.

HR-QOL was measured using the SF 36 form, which allows the results to be expressed under eight scales. Raw scores were transformed and aggregated into two summary measures: physical component summary (PCS) and mental component summary (MCS) scales (13). The domains included in the PCS scale are physical functioning, role physical, bodily pain, general health, and vitality. The domains included in the MCS scale are general health, vitality, social functioning, role emotional, and mental health (13). If a subject failed to answer

any single item, a numeric value equal to the average score for the same scale to which the item belonged was imputed only if at least 50% of the items were answered. If there were insufficient responses to compute more than one of the eight scales, the aggregate PCS and/or MCS were coded as missing.

Statistical Analyses

Continuous variables are expressed as mean and SD, or median with interquartile (IQR), as appropriate. The significance of difference between continuous variables was tested using either *t* test, one-way ANOVA, Mann-Whitney rank-sum, or Kruskal-Wallis test, as appropriate. The difference in the distribution of categorical variables was tested using the chi-square test. Associations were tested using Spearman rank sum test.

Univariate association of total pill burden was tested with the following variables: age; gender; race/ethnicity; center; dialysis vintage; dialysis modality; previous transplant history; Charlson's co-morbidity index; total number of medications; corrected serum calcium, phosphorus, PTH, albumin, and bicarbonate levels; and Kt/V. In addition to these 15 variables, associations of PCS and MCS, adherence to phosphate binders, and serum phosphorus level were tested with each other and with total pill burden and pill burden from phosphate binders. All predictors with a *p*-value of <0.10 for each of the five dependent variables on univariate analyses were entered into the relevant multivariate linear regression models; center was forced into each of the models tested. Step-wise selection was used to identify the variables to be entered into the model, and goodness of fit was determined by visual inspection of log P-P plots. A *p*-value of <0.05 was considered statistically significant.

Given the significantly lower response rate at center 3, sensitivity analysis was performed by repeating all of the univariate and multivariate analyses described above after excluding the participants from that center.

Results

Subject Characteristics

At center 1, 154 of the 205 (75%) eligible subjects were enrolled; at center 2, 67 of 90 (74%) eligible subjects were enrolled; and at center 3, 28 of 150 (19%) eligible subjects were enrolled. Sixteen subjects did not complete the study: 12 at center 1, one at center 2, and three at center 3. Thus, a total of 233 subjects formed the study cohort. The key characteristics of the cohort are summarized in Table 1. The mean age and gender distribution of subjects at the three sites was similar, but there were significant differences in race/ethnicity of participants (Table 1). Furthermore, subjects in center 3 had significantly longer dialysis vintage and the highest co-morbidity burden.

The cohort took a mean of 11 ± 4 medications (nine oral + two parenteral); the oral medications contributed to a median daily pill burden of 19 (IQR, 12). There were center differences such that subjects in center 3 had the highest medication number and pill burden. The daily pill burden exceeded 10 in 91% of subjects, was more than 20 in 47%, and more than 30 in 17% (Figure 1). The results of univariate analyses to identify the predictors of total pill burden are summarized in Table 2. On multivariate, linear regression analyses, pill burden was significantly higher among subjects undergoing peritoneal dialysis; in addition, higher pill

Table 1. Patient characteristics, quality of life, and adherence

	Center 1	Center 2	Center 3	Entire Cohort
Sample Size ^a	142	66	25	233
Demographics				
Age, years	52.0 ± 14.4	53.8 ± 16.0	55.4 ± 13.0	52.9 ± 14.7
Gender, % males	58	58	56	58
Race/Ethnicity, n (%) ^a				
Non-Latino Whites	10 (7)	18 (27)	13 (52)	41 (18)
Non-Latino Blacks	31 (22)	23 (35)	12 (48)	66 (28)
Latino	72 (51)	18 (27)	0 (0)	90 (39)
Others	29 (20)	7 (11)	0 (0)	36 (15)
Dialysis vintage, years ^b	3.1 (5.3)	2.9 (4.1)	5.3 (9.4)	3.1 (5.3)
Modality, n (%) ^a				
In-Center hemodialysis	119 (84)	43 (65)	22 (88)	184 (79)
Peritoneal dialysis	23 (16)	19 (29)	2 (8)	44 (19)
Home hemodialysis	0 (0)	4 (6)	1 (4)	5 (2)
Charlson's Co-morbidity Score ^a	4.8 ± 2.2	5.7 ± 2.7	7.1 ± 3.2	5.3 ± 2.6
Laboratory data				
Corrected serum calcium, mg/dl ^a	9.4 ± 0.6	8.9 ± 0.5	9.1 ± 0.6	9.2 ± 0.6
Serum phosphorus, mg/dl ^b	5.2 (1.4)	5.1 (1.5)	5.7 (1.8)	5.2 (1.4)
Serum parathyroid hormone, pg/ml ^b	264 (176)	298 (268)	208 (277)	273 (218)
Serum bicarbonate, meq/L ^a	27 ± 3	22 ± 3	24 ± 3	25 ± 3
Serum albumin, g/dl ^a	3.9 ± 0.5	3.6 ± 0.4	3.8 ± 0.4	3.8 ± 0.5
Kt/V				
In-Center hemodialysis ^a	1.88 ± 0.35	1.65 ± 0.35	1.44 ± 0.31	1.78 ± 0.38
Peritoneal dialysis, weekly ^b	2.62 (0.97)	2.60 (1.21)	1.84 (-)	2.53 (1.12)
Home hemodialysis ^b	-	2.14 (0.35)	0.58	2.03 (1.04)
Quality of life (SF36)				
Physical Component Score	39.4 ± 8.7	36.6 ± 10.4	37.3 ± 10.9	38.4 ± 9.5
Mental Component Score ^a	43.4 ± 10.3	46.5 ± 12.6	48.5 ± 10.6	44.8 ± 11.2
Pill burden and adherence				
Total medication number, n ^{ab}	10 ± 4	11 ± 3	17 ± 5	11 ± 4
Total pill burden, n ^{ab}	17 (10)	21 (14)	25 (14)	19 (12)
P-Binder, patient number (%)				
Sevelamer hydrochloride ^a	116 (82)	37 (56)	19 (79)	172 (74)
Lanthanum carbonate	9 (6)	8 (12)	1 (4)	18 (8)
Calcium-based binders ^a	28 (20)	32 (49)	9 (38)	69 (30)
P-binder pill burden, n ^b	9 (6)	9 (8)	8 (4)	9 (6)
P-binder pills, % of total pill burden ^a	53 ± 18	47 ± 19	33 ± 20	49 ± 19
Adherence to P-binders, ^b %	68 (57)	70 (43)	89 (27)	70 (52)
Prevalence of non-adherence, % ^{ac}	66	67	32	62

Data expressed as mean ± standard deviation, except where indicated

^a $P < 0.05$, for difference between three centers

^bData expressed as median and interquartile range

^cAdherent, Adherence, 80% to 120% of expected

burden was independently associated with a higher total number of medications, longer dialysis vintage, and lower serum bicarbonate levels. In analyses limited to subjects

undergoing in-center hemodialysis (HD), lower Kt/V, but not serum bicarbonate levels, was an additional predictor of higher total pill burden.

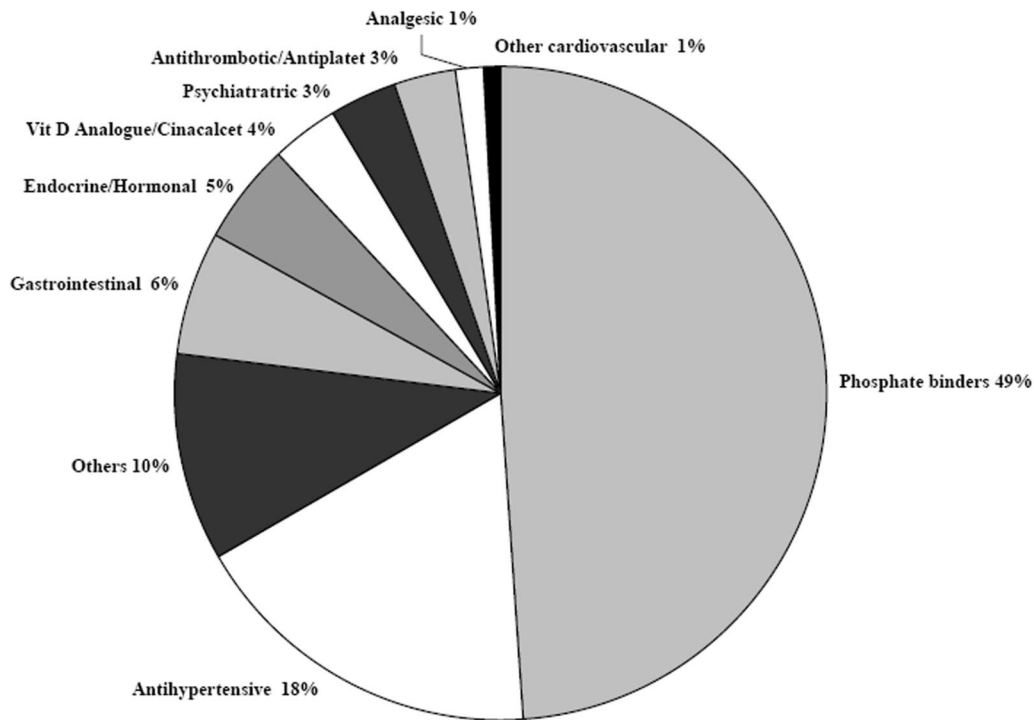


Figure 2. Percentage of pill burden from different classes of medications.

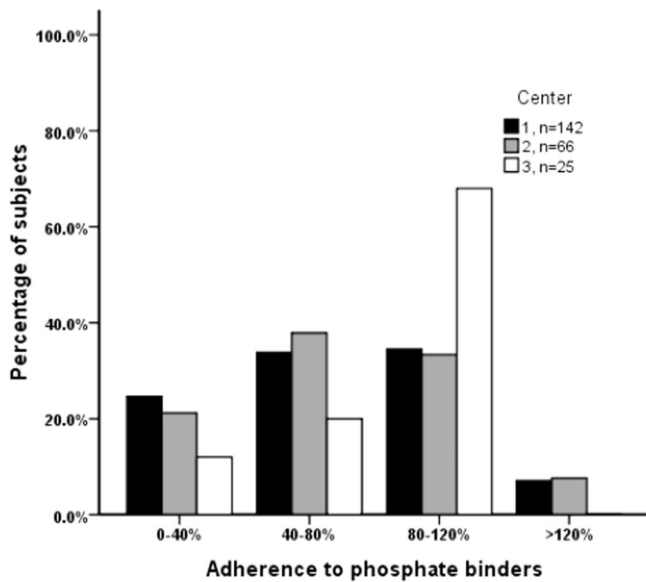


Figure 3. Distribution of patients by centers, based on adherence to phosphate binders from pill count at the time of the study visit. Subjects were deemed to be adherent if they consumed 80% to 120% of the expected pill count.

medications. The median adherence in the study cohort was 72% (IQR, 50).

To identify predictors of adherence to phosphate binders, subjects were excluded with >120% adherence to prescribed therapy. There was a significant inverse relationship between adherence to phosphate binders and pill burden from phosphate binders ($r = -0.19, P = 0.006$). Data were examined after

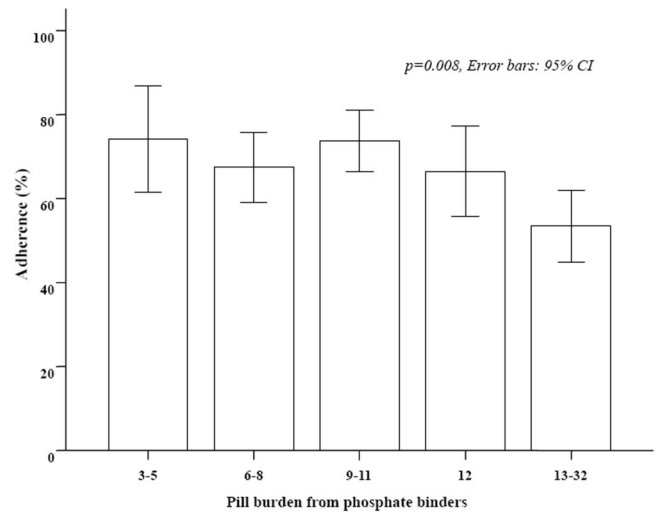


Figure 4. Adherence to phosphate binders in subjects grouped into quintiles of pill burden from phosphate binders.

dividing subjects into quintiles based on pill burden from phosphate binders; the trend, while significant ($P = 0.008$), appeared nonlinear, with decrease in adherence only when the daily pill burden from phosphate binders exceeded 12 (Figure 4). Additional predictors of adherence on univariate analyses were age and serum albumin (Table 2). Two different multivariate models to identify predictors of adherence were run: one included total pill burden, and the other included pill burden from phosphate binders (Table 3).

The median serum phosphorus levels in the cohort were 5.2 mg/dl (IQR, 1.4); serum phosphorus levels were >5.5 mg/dl in

Table 3. Multivariate analyses for the predictors of adherence to phosphate binders

	Model 1 $R = 0.37, P < 0.001$		Model 2 $R = 0.35, P < 0.001$	
	Beta	<i>p</i> value	Beta	<i>p</i> value
Center 2 (ref center 1)	0.08	0.25	0.08	0.26
Center 3 (ref center 1)	0.14	0.04	0.20	0.005
Pill burden from phosphate binders	-0.19	0.003	-	-
Total pill burden	-	-	-0.15	0.03
Age, per 1 yr	0.22	0.001	0.20	0.001
Serum albumin, per 1 g/dl	0.28	<0.001	0.25	0.001

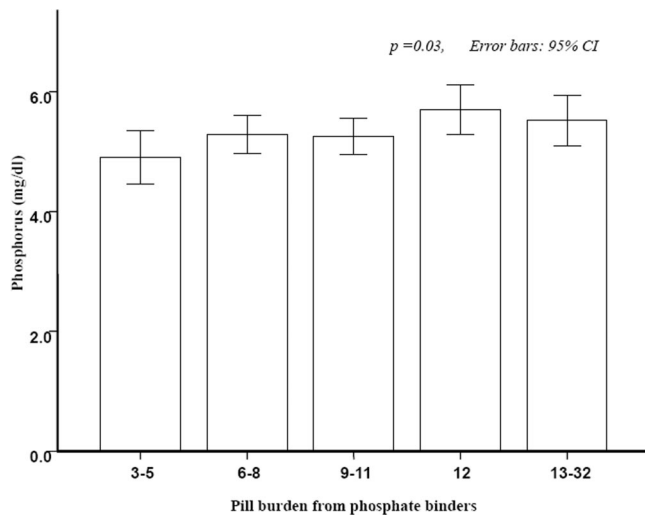


Figure 5. Mean serum phosphorus levels in subjects grouped into quintiles of pill burden from phosphate binders.

39% of study participants. There was a significant direct relationship between serum phosphorus levels and pill burden from phosphate binders ($r = 0.16, P = 0.01$). There was a modest but significant increase in serum phosphorus levels with increasing quintiles of pill burden from phosphate binders (Figure 5). Other predictors of serum phosphorus levels on univariate analyses are summarized in Table 2. On multivariate, linear regression analysis, higher serum phosphorus levels were independently associated with greater pill burden from phosphate binders, higher serum PTH level and MCS score, and lower bicarbonate levels. There was no significant association between adherence to phosphate binders and serum phosphorus levels on either univariate or multivariate analyses.

Data for normalized protein equivalent of nitrogen appearance (nPNA) were available for 186 subjects (142 HD, and 44 peritoneal dialysis). There was a significant direct relationship between nPNA and serum phosphorus levels. On multivariate analyses, there was no significant association between nPNA and serum phosphorus levels.

Sensitivity Analyses

After excluding data of participants from center 3, the median pill burden was 19 (IQR, 11). There remained a significant

association between pill burden and PCS score of HR-QOL on both univariate ($r = -0.18, P = 0.01$) and multivariate analyses ($P < 0.001$). Phosphate binders accounted for $51 \pm 18\%$ of the total pill burden. Only 34% of subjects were adherent to phosphate binders in the two centers. An inverse association between pill burden from phosphate binders and adherence to these drugs persisted in these sensitivity analyses ($r = -0.21, P = 0.004$), an association that persisted on multivariate analysis as well ($P < 0.001$). Similarly, a higher pill burden was associated with higher serum phosphorus levels on both univariate ($r = 0.17, P = 0.02$) and multivariate analyses ($p < 0.001$). There was no significant relationship between adherence and serum phosphorus levels.

Discussion

This study highlights several issues that are potentially important to improve the management of maintenance dialysis patients. The daily pill burden in these patients is very high, and almost one-half of patients were prescribed to take over 20 pills daily. A higher pill burden was an independent predictor of lower scores on the physical dimensions of the HR-QOL. Phosphate binders accounted for one-half of the daily pill burden, and a higher pill burden from phosphate binders was associated with a significantly lower adherence and higher serum phosphorus levels. However, a relationship between adherence to phosphate binders and serum phosphorus levels was unable to be demonstrated.

The median number of medications prescribed to this study's cohort is similar to what has been reported in previous studies of dialysis patients (10). However, to the authors' knowledge, this is the first study to focus on the very high pill burden in maintenance dialysis patients. This study is likely to be externally valid since it was conducted at clinics located at three geographically distinct centers in the country. How high the burden of 19 pills daily is best understood by comparing it with the reported daily pill burden among patients with other chronic diseases: diabetes mellitus, two to four pills/d, and congestive heart failure, 10 to 11 pills/d (14,15). Pill burden has been best characterized in patients with acquired immune deficiency syndrome (AIDS). The daily pill burden is less than 20 with most regimens that include nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, or protease inhibitor (16). Thus, the daily pill burden of mainte-

nance dialysis patients appears to be among the highest among patients with various chronic diseases (almost one-half of patients were prescribed over 20 pills, and about one-quarter were prescribed more than 25 pills daily). The pill burden was somewhat higher in patients undergoing chronic peritoneal dialysis. Some medications, such as vitamin D receptor activators that are given parenterally in maintenance hemodialysis patients, need to be given orally in peritoneal dialysis patients, which probably accounts for the difference.

In addition to the high potential for drug interactions, it was found that the high total daily pill burden was an independent predictor of low scores on the physical dimensions of the HR-QOL. Although patients with a greater burden of co-existing illnesses have a higher pill burden, the association of the latter with HR-QOL was independent of other measures of overall health, such as advancing age, Charlson's co-morbidity index, and serum albumin on multivariate analyses. Thus, this study suggests that total daily pill count may capture additional information about the burden of disease and health of dialysis patients over and above that provided by co-morbidity measures or symptom burden. Whether total pill burden is an independent predictor of patient morbidity and mortality has not been studied to date and needs to be investigated in future studies.

The authors further examined if the high pill burden was associated with patient adherence to therapy. Since phosphate binders accounted for about one-half of daily pill burden, the assessment of adherence was limited to this class of drugs. Furthermore, the authors sought to determine if pill burden and adherence had any tangible relationship with a biologically important measure in dialysis patients, such as serum phosphorus levels. Only 38% of subjects in the study cohort were adherent to phosphate binders (consuming 80% to 120% of pills prescribed), similar to other reports (12). A higher pill burden was associated with lower adherence to therapy, an association that persisted on multivariate analyses. This finding is consistent with previous findings that complexity of regimens impair adherence to therapy (17).

It appears reasonable to conclude that reducing pill burden may improve patient adherence. There are two components of pill burden: number of tablets to be taken at a given time and the frequency of administration. In disease states like hypertension, it is often recommended that patients should be prescribed the smallest number of medications (including fixed-dose combinations) that need to be taken preferably once, but no more than twice, daily (18). However, the frequency of administration cannot be reduced with any of the currently available phosphate binders; in a recent clinical trial, once daily administration of sevelamer hydrochloride was inferior to doses administered thrice daily (19). The number of tablets taken each time is a second, and potentially modifiable, component of pill burden. Patients treated with lanthanum carbonate had the lowest pill burden and those with combination therapy the highest in the study cohort. The relationship between adherence and pill burden appeared to be nonlinear such that the greatest fall-off in adherence occurred in patients prescribed 12 or more phosphate binder pills per day. It has been

shown that lower pill burden is also associated with greater patient satisfaction (20), and thus it seems prudent that patients should not be prescribed more than 12 phosphate binder pills daily. However, the current study only tested associations, and it is unclear if lower pill burden will translate into a higher adherence.

Over the last few years, serum phosphorus has been recognized as an independent risk factor for all-cause and cardiovascular mortality in individuals with and without chronic kidney disease (21–23). Thus, aggressive management of hyperphosphatemia is an important component of the management of maintenance dialysis patients. In this study cohort, higher pill burden was an independent predictor of hyperphosphatemia. However, the study was unable to demonstrate any relationship between adherence to therapy and serum phosphorus levels on either univariate or multivariate analyses. These two factors suggest that the physicians responded to uncontrolled serum phosphorus by prescribing a larger number of phosphate binders, and in nonadherent patients, a higher pill burden may have served to compensate for their nonadherence. However, the higher pill burden did not translate into better control of serum phosphorus levels, suggesting that increasing the number of prescribed phosphate binders may be an inappropriate response to hyperphosphatemia in many patients. The data were further analyzed to identify additional, potentially modifiable, predictors of serum phosphorus so that effective therapies may be devised. First, higher PTH levels were associated with serum phosphorus levels. The direction of relationship between the two parameters has long been argued, but it is likely to be bidirectional. Thus, in many patients with uncontrolled serum PTH levels, a higher efflux of phosphorus from the bone may contribute to higher serum phosphorus levels, a problem not readily corrected by a higher pill burden from phosphate binders. Second, evaluation was made to determine if a higher protein intake (nPNA), and thus a higher phosphorus intake, was associated with higher serum phosphorus. Any independent association between nPNA and serum phosphorus levels on multivariate analyses was unable to be demonstrated.

This study is not without limitations. First, the recruitment rate in one of the three centers was significantly lower and patients recruited from this site had the highest adherence rate. This raises the possibility of selection bias in the study subjects enrolled from that site. To limit the bias, the center was forced into all multivariate models presented herein. Furthermore, there was no significant difference in the results even when data from center 3 were excluded (sensitivity analyses). Second, pill counting as a method of assessing adherence has its limitations and may underestimate the magnitude of the problem in dialysis patients. Furthermore, the date when the drug was dispensed by the pharmacist was considered to be the date when the patient was expected to start taking medications from that bottle. This may have led to overestimation of nonadherence. However, this error is likely to be randomly distributed and not affect the associations presented herein. Third, data for Kt/V and nPNA were not available for all patients.

In summary, this is the first study to report on the pill burden

of dialysis patients, which appears to be the highest of any chronic disease state published to date. This pill burden was associated with a lower HR-QOL, independent of the Charlson's co-morbidity index and thus may be an independent measure of burden of disease on individuals. Phosphate binders, as a leading contributor, accounted for half of the daily pill burden; higher pill burden was associated with significantly lower adherence. There appear to be many factors operative in patients that lead to uncontrolled serum phosphorus levels. Increasing the number of pills prescribed is unlikely to be effective in many patients and may come at a cost of poorer HR-QOL.

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