Managing Phosphate Burden in Patients Receiving Dialysis: Beyond Phosphate Binders and Diet

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Most patients receiving dialysis rely on dietary restriction and phosphate binders to minimize the risk of hyperphosphatemia, which is associated with increased mortality. However, dietary restriction is difficult because of hidden phosphate additives in processed foods and medications. Restriction of dietary phosphate sources such as protein may increase the risk of malnutrition. Phosphate binders, the only pharmacologic option for phosphate management since aluminum salts were introduced several decades ago, are often insufficient for binding the 1400–2500 mg of phosphate potentially consumed daily. Over the last decade, serum phosphate levels in the United States have risen, and >69% of patients receiving dialysis exhibited a most recent phosphate level >4.5 mg/dl (above the normal range), indicating an urgent need for new, more effective therapies to manage phosphate burden. Novel, nonbinder therapies such as transcellular and paracellular phosphate absorption inhibitors may be used for phosphate management, and future studies should examine whether they allow fewer dietary restrictions for patients receiving dialysis, potentially improving patient quality of life and nutritional status. It is imperative that we collaborate to move beyond the restrictive approaches available today and provide patients and clinicians with an array of strategies so that they may choose the most appropriate patient-centered therapy.

There Is an Urgent Need for New Classes of Phosphate-Lowering Therapies

CKD is estimated to affect 15% of the adult population in the United States.[1] In the later stages of CKD, phosphate retention occurs because compensatory biologic mechanisms that both limit phosphate absorption and increase phosphate excretion become insufficient to maintain phosphate homeostasis, which may lead to hyperphosphatemia.[2] Elevated serum phosphate levels are associated with several adverse outcomes including vascular calcification, cardiovascular disease, secondary hyperthyroidism, and an increased risk of all-cause mortality.[3–6] Patients with CKD G3a-G5d are advised to lower phosphate levels toward the normal range.[3] However, there is still a lack of data that show an improvement in clinical outcomes when interventions aimed at lowering serum phosphate are used in patients with CKD.[3] Today, approximately 600,000 patients with ESKD are undergoing dialysis in the United States,[1] most of whom likely rely on dietary restrictions and phosphate binders to avoid the negative consequences of phosphate retention and hyperphosphatemia.

Although dietary restrictions are a foundational part of phosphate management, sustained adherence can take a toll on patients. Patients receiving dialysis are typically advised by dietitians and nephrologists to adhere to a diet low in phosphate, potassium, sodium, and liquids to avoid the negative consequences associated with electrolyte overload.[7] While updated Kidney Disease Outcomes Quality Initiative guidelines acknowledge the need to create individualized dietary plans based on patient needs and clinical judgment, with consideration given to the bioavailability of dietary phosphate sources, these nutritional guidelines no longer specify a target phosphate intake range because of a lack of demonstrated clinical efficacy for target-based strategies.[8] To decrease the risk of hyperphosphatemia and electrolyte overload, patients receiving dialysis cannot consume a long list of otherwise healthy foods, and there is concern that

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many patients receiving dialysis do not consume a heart-healthy diet.[9] Phosphorus and protein intake correlate significantly; thus, a major risk of certain restrictive diets is protein malnutrition.[10] Along with the stress of daily self-management, dietary restrictions can negatively affect the quality of life of patients by limiting family and social interactions.[11]

The burden of constant dietary self-management is exacerbated by the ubiquity of hidden phosphate additives in modern processed foods and in medications. Dietary phosphates may be considered hidden because manufacturers are not required to include the quantity of phosphate from food additives on labels.[7,12] The reality of industrialized food systems with insufficient food labeling practices and the resultant challenge that presents to managing dietary phosphate sources is reflected in language added in the 2020 updates to the nutritional guidelines provided by Kidney Disease Outcomes Quality Initiative. New guidance states that individualized dietary management plans should also take into consideration the source of dietary phosphate because the bioavailability of phosphate may vary between organic (animal or vegetal) and inorganic (food additives) sources.[8] While absorption of phosphate from organically derived foods do vary depending on the source, the inorganic phosphate from additives used in processed foods is more readily absorbed than organic sources overall.[12,13] Quantities of inorganic phosphate that may also be present as inactive ingredients in medications which are not required to be disclosed provide yet another hidden source of phosphate. However, medicinal sources have the potential to represent a significant contribution to the sum phosphate intake for dialysis patients because medicines commonly prescribed to patients at dialysis clinics in the United States may contain up to 200 mg phosphate/tablet.[14,15]

Unlike treatments for some disease states that regularly see innovations in therapeutic classes, phosphate binders have been the only pharmacologic option to manage phosphate burden since aluminum salts were introduced in the 1970s.[16,17] (Figure 1) Although phosphate binders are shown to effectively reduce serum phosphate concentrations in patients receiving dialysis,[18–20] the binding capacities of each pill could be maxed out in the face of high dietary phosphate intake. Binding capacities for the

recommended starting daily dose of each binder ranges from 63 to 234 mg of phosphates (Table 1).[18–22] Even high doses of phosphate binders can typically only remove up to 300 mg of phosphate per day.[12] This is insufficient to keep up with an estimated daily dietary phosphate load of 1400–2500 mg[23–25] (Figure 2).

Phosphate binders can negatively affect patient quality of life in a variety of ways. The addition of phosphate binders to an already extensive medication regimen can substantially increase pill burden. Chiu *et al.* found that phosphate binders account for approximately 50% of the total daily pill burden for patients receiving dialysis, with a median daily count of nine phosphate binder pills, and many may take up to 15–20 binders per day.[26] This study of the effect of pill burden on quality-of-life outcomes in dialysis patients reported that only approximately 40% of patients were adherent to the phosphate binder therapy,[26] potentially because regularly taking high quantities of large, hard-to-swallow pills may be both unpleasant and logistically difficult for patients. Patients must take many binders with each meal and snack, and timing pill ingestion is critical for binders to work as well, and patients may easily forget to take binders on time, particularly if they are at work, at a restaurant, or away from home. In addition to the pill burden phosphate binders may add with each meal and snack, they are also associated with gastrointestinal adverse events, most commonly nausea, vomiting, diarrhea, and constipation[18–20,27] (Figure 3). An analysis of reasons for phosphate binder discontinuation found that 11% of patients stopped treatment because of nontolerance, and within this subgroup, 48% discontinued because of gastrointestinal upset.[28]

Despite extensive dietary restriction and prescription of phosphate binders, phosphate control has worsened for patients with CKD in the United States over recent years. Of patients receiving dialysis in January 2021, 69% were found to have serum phosphate levels above normal range (>4.5 mg/dl), and the mean phosphate levels in patients receiving dialysis was 5.6 mg/dl after having seen a decrease in phosphate levels over the decade spanning 2002–2012.[29,30] While the most recent Kidney Disease Improving Global Outcomes guidelines (2017) did not provide specific serum phosphate targets, it is recommended that patients with CKD G3a-G5D with persistently elevated
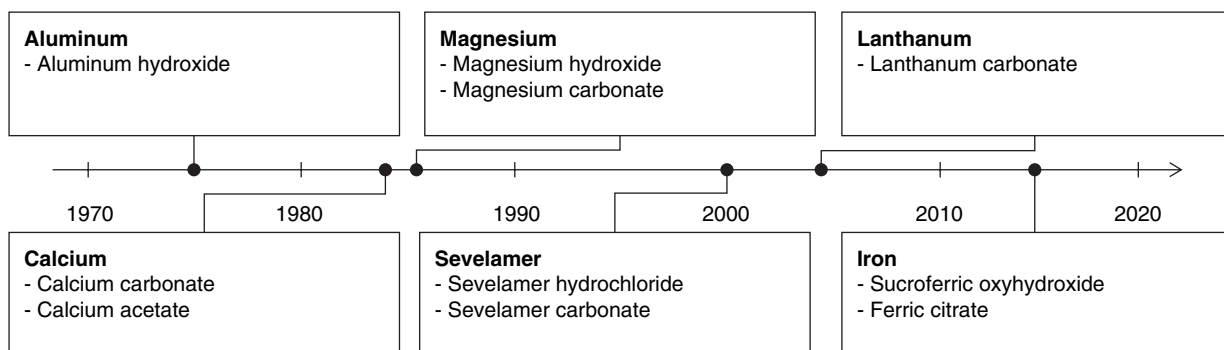

Figure 1. Timeline of phosphate management strategies. Over the last 50 years, minor changes in the phosphate binder drug class have been introduced through use of different active ingredients.

Table 1. Recommended dose and binding capacities for select phosphate binders

Phosphate Binder	Recommended Starting Dose (per day)	Binding Capacity (mg Phosphate/ g Binder)	Daily Binding Capacity of Starting Dose
Sevelamer carbonate[20–22]	3–6× 0.8 g pills or 0.8 g packets	26.3 mg/g	63–126 mg
Lanthanum carbonate[18,22]	3× 0.5 g pills or 2× 750 mg packets	78–156 mg/g	117–234 mg
Calcium acetate[19,21]	6 gelcaps (667 mg calcium acetate/gelcap)	45 mg/g	180 mg

phosphate levels should lower levels toward a normal range of 2.8–4.5 mg/dl.[3,30] This lack of improvement in overall patient phosphate levels suggests that current therapies for phosphate management are not effective for all patients receiving dialysis. Thus, there is a clear and urgent need for new classes of therapies for phosphate management to improve outcomes.

New Classes of Phosphate Management Therapies Would Give Patients and Clinicians Freedom of Choice

New phosphate-lowering therapies that reduced both pill burden and adverse events could potentially improve patient quality of life and may help patients reach therapeutic goals. The effect of treatment innovation has been demonstrated in potassium management, where within the past decade, two different potassium binders have been developed for daily use that are safe and well-tolerated.[31,32] These new agents have become enablers of life-saving/kidney-preserving agents like renin–angiotensin aldosterone inhibitors that normally could not be given to people with stages 4 and 5 CKD.[33,34]

New classes of therapies for phosphate management are being developed that instead of binding ingested phosphates, target one of two intestinal phosphate absorption pathways: the paracellular or transcellular pathway (Figure 4).[2,35–39] In brief, the transcellular absorption pathway uses specific phosphate transporters such as the sodium-dependent phosphate cotransporter 2b (NaPi2b) and type-III inorganic phosphate (Pi) transporters PiT-1 and PiT-2, whereas the paracellular pathway relies on the passive transport of phosphate through tight junction complexes between cells according to concentration gradients.[2,40] Because these therapies have different mechanisms of action from that of phosphate binders, there is hope that they will provide necessary therapeutic innovation.

Several transcellular phosphate absorption inhibitors are in development, and clinical trial data so far are mixed. A phase 1 trial on standardized phosphate diet of the novel drug EOS789, an inhibitor of NaPi-2b, PiT-1, and PiT-2, demonstrated encouraging results in patients receiving hemodialysis.[35] Nicotinamide seems to inhibit gastrointestinal NaPi2b cotransporters, thereby reducing phosphate-specific transcellular permeability.[36] However, there was a lack of significant reductions in phosphate or FGF23 in nondialysis patients with CKD treated by lanthanum carbonate and/or nicotinamide during a 12-month trial.[37] A phase 1 study of the NaPi2b inhibitor ASP3325 showed that this therapy was not effective in reducing serum phosphate levels in patients with ESKD.[38]

Studies have shown that the paracellular pathway is the predominant pathway of intestinal phosphate absorption in
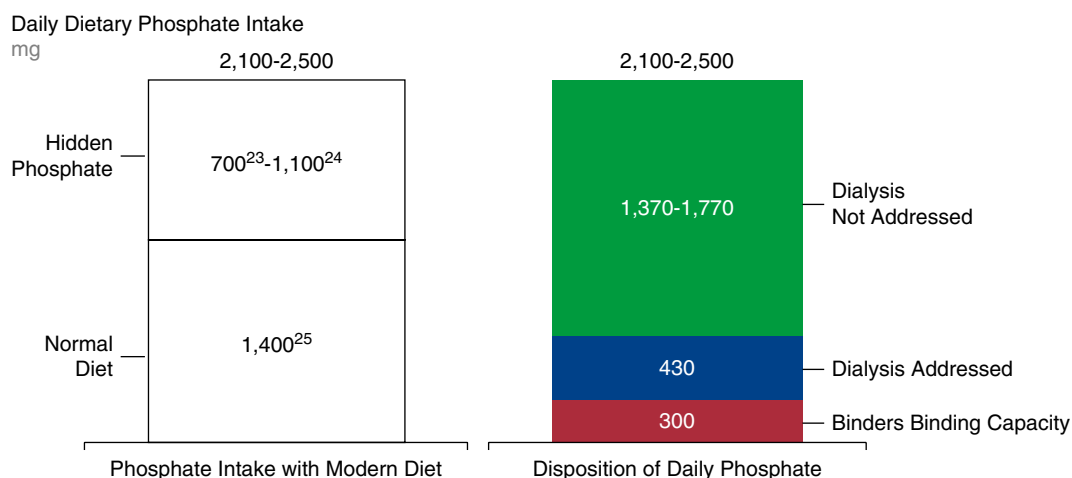

Figure 2. Phosphate binders are insufficient to match daily dietary phosphate intake.[18–25,48] The binding capacity of phosphate binders is too low to account for daily phosphate intake, particularly for diets high in hidden phosphates.
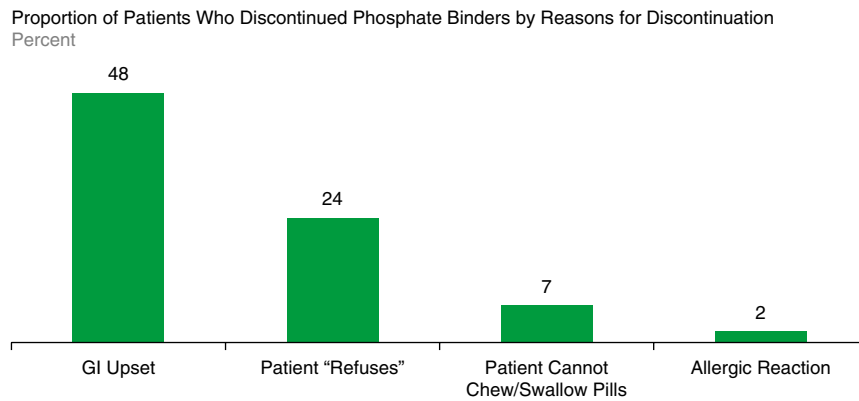
Proportion of Patients Who Discontinued Phosphate Binders by Reasons for Discontinuation
Percent

Figure 3. Reasons for phosphate binder discontinuation.[28] Approximately half of patients who discontinued phosphate binders cited gastrointestinal (GI) upset as the reason for discontinuation.

humans.[41–43] Tenapanor (Ardelyx Inc.) is a paracellular phosphate absorption inhibitor that has been shown to reduce serum phosphate concentrations in clinical trials. Its mechanism of action inhibits the sodium/hydrogen exchanger isoform 3 in the gastrointestinal tract, which blocks paracellular phosphate permeability by reducing sodium absorption and increasing intracellular proton retention, causing conformational changes in tight junction proteins.[41] In a phase 3 study of ESKD patients with hyperphosphatemia receiving maintenance dialysis, tenapanor administration (after a phosphate binder washout period) lowered serum phosphate by ≥1.0 mg/dl at 8 weeks in each of the three dose groups studied.[39] The results from a similarly designed, long-term phase 3 study showed that at 26 weeks, tenapanor administered as one tablet twice a day as a replacement therapy to phosphate binders lowered serum phosphate in participants ($n=248$) from baseline concentrations by a mean (SD) of 1.4 (1.8) mg/dl.[44] These studies indicate that twice-daily tenapanor could potentially replace phosphate binders, thereby substantially reducing pill burden. However, no prespecified head-to-head analyses comparing tenapanor as monotherapy compared with other phosphate control therapies have been conducted.

Tenapanor administered in conjunction with phosphate binders can have a more significant effect than binders alone. Data from a trial that compared the effectiveness of a combination of tenapanor and binder versus placebo and binder showed that tenapanor plus binder resulted in a 0.65 mg/dl larger mean serum phosphate reduction from baseline compared with placebo plus binder.[45] The study included 236 patients undergoing maintenance dialysis with hyperphosphatemia (defined in this trial as serum phosphate 5.5–10 mg/dl inclusive), despite receiving phosphate binder therapy (sevelamer, nonsevelamer, sevelamer plus nonsevelamer, or multiple nonsevelamer binders).[45] In addition, almost twice as many patients treated with tenapanor and binder achieved serum phosphate <5.5 mg/dl compared with patients treated with placebo and binder (37%–50% versus 18%–24%, $P < 0.05$).[45]
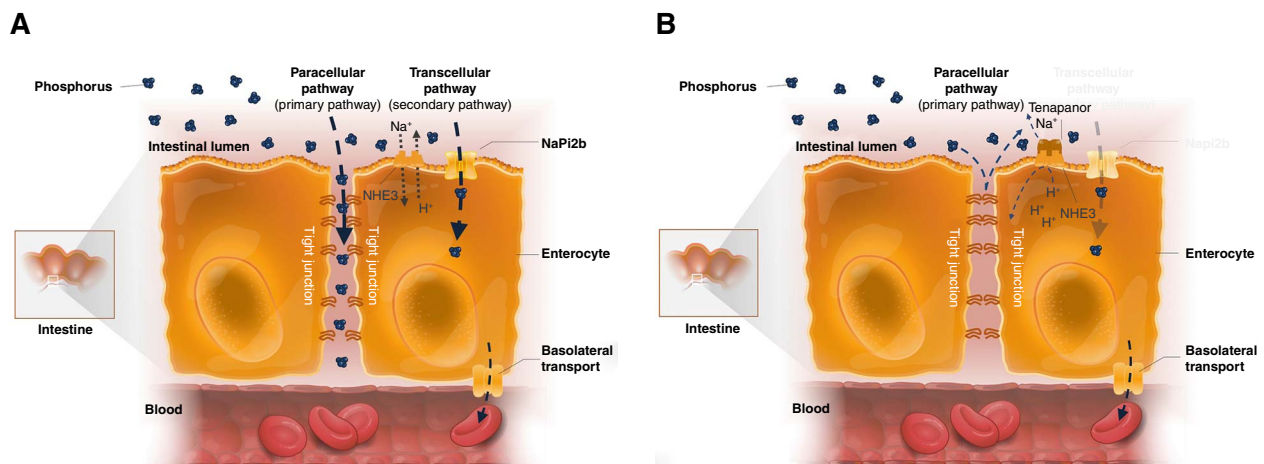

Figure 4. Intestinal phosphate absorption pathways.[2] (A) Intestinal phosphate absorption occurs through the transcellular and paracellular pathways. Absorption through the secondary transcellular pathway is facilitated by the sodium-dependent phosphate transporter NaPi2b. In the primary paracellular pathway, phosphate is absorbed passively along the concentration gradient through tight junctions. (B) Tenapanor reduces permeability of tight junctions to phosphate, reducing paracellular phosphate absorption. NaPi2b, sodium-dependent phosphate transporter 2b; NHE3, sodium/hydrogen exchanger isoform 3.
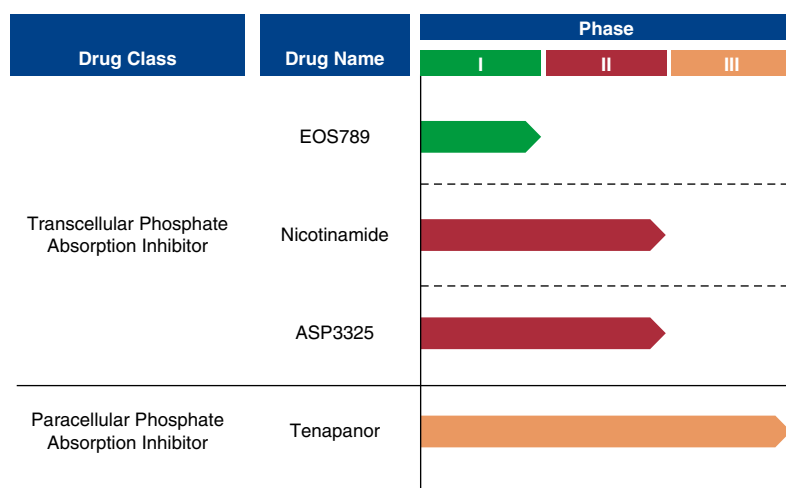
Figure 5. Phosphate absorption inhibitor trials. Two new classes of phosphate management drugs, transcellular and paracellular phosphate absorption inhibitors, are in development.

This dual-mechanism approach may be particularly relevant for patients with persistent hyperphosphatemia.[45]

It should be noted, that while tenapanor has been shown to effectively reduce serum phosphate in most patients,[39,44,45] a clinical benefit of tenapanor for patients with CKD has not been established, as is the case with other serum phosphate-reducing medications, including phosphate binders.[3] While tenapanor was safe and generally well-tolerated (as a monotherapy or in combination with other binders), in the published studies to date, 5%–7% of patients who either switched to tenapanor or added tenapanor to a preexisting phosphate binder regimen discontinued because of hyperphosphatemia, and 4%–20% discontinued because of adverse events or tolerability issues.[39,44,45] Diarrhea has been the most common adverse event in these studies and was mostly reported as mild to moderate in severity.

Despite the potential for adverse events and the relatively small population of nonresponders, tenapanor has positive effects on patient-reported outcomes. Preliminary data from congress presentations of the OPTIMIZE trial show that 85.4% of patients with hyperphosphatemia previously treated with binders who switched to a new treatment plan that reduced their binder dose by ≥50% and added tenapanor (30 mg twice daily) reported an improvement in their overall phosphate management experience.[46] The primary reason attributed to a change in perception was a change in medication burden, related to a reduction in the size, number, frequency, or diversity of pills patients used to manage phosphate.[46] (Figure 5) Preliminary efficacy results from the OPTIMIZE trial show that serum phosphate was lowered to <5.5 mg/dl in approximately half of all participants that either added tenapanor to a 50% reduced binder regimen or switched completely to only tenapanor.[47]

New Treatment Options Could Give Patients the Freedom to Eat More Healthy Foods and Improve Their Quality of Life

Given the need for improved phosphate control in patients receiving dialysis and the lack of treatment choice regarding classes of agents, new therapies with alternative mechanisms of action are needed to broaden the armamentarium for hyperphosphatemia therapy. New classes of pharmacologic therapies would also allow for combination therapies, with the dual benefits of possibly improving efficacy while lowering potential side effects. Furthermore, the benefit to patient health outcomes vis-à-vis lower phosphate concentrations and potentially lower cardiovascular event rates only describes the clinical/medical side of patient care. The average hemodialysis patient may take 20 pills/d with phosphate binders comprising approximately half the pill burden.[26] The addition of phosphate transport blockers to replace all or a portion of the phosphate binder regimen could significantly reduce pill burden.

Often overlooked from the patient's point of view is significantly improved quality of life that would result from additional freedom of food choices and meals if more effective pharmacologic interventions were available. Importantly, more flexible protein intake would also reduce the risk of malnutrition and protein-energy wasting. In addition, patients would experience the social and emotional benefits of being able to participate in meals with family and friends again, instead of preparing and eating separately. We should strive to allow patients and their clinicians the opportunity to tailor appropriate combinations of therapeutic approaches from as wide a field of choices as possible, provided these therapies are deemed safe and effective in reducing serum phosphate in patients with CKD who are receiving dialysis.

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Data Sharing Statement

All data is included in the manuscript and/or supporting information.

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