

Class Review: Vitamin D Analogs

Date of Review: January 2017

Purpose for Class Review:

Oral and intravenous (IV) vitamin D analogs are important treatment options for secondary hyperparathyroidism and low levels of vitamin D associated with chronic kidney disease (CKD). Evidence on effectiveness and harms will be reviewed to make recommendations to the Oregon Health Authority (OHA) on criteria for use.

Research Questions:

1. In children and adult patients with CKD, what is the evidence for differences in efficacy or effectiveness (i.e., parathyroid hormone changes, mortality, cardiovascular outcomes, need for renal replacement therapy) between vitamin D analogs used for the treatment of secondary hyperparathyroidism?
2. In children and adult patients with CKD, what is the evidence for differences in harms (i.e., hypercalcemia, hyperphosphatemia) between drug therapies used for the treatment of secondary hyperparathyroidism?
3. Are there subpopulations (i.e., different stages of chronic kidney disease, dialysis requirements, socioeconomic status, age, race, ethnicities) in which one vitamin D analog may be more effective or associated with less harm than other vitamin D analog for the treatment of secondary hyperparathyroidism?

Conclusions:

- The evidence review on vitamin D analogs found 4 systematic reviews and meta-analyses, 3 randomized-controlled trials and 3 clinical practice guidelines from the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD), National Institute for Health and Care Excellence (NICE), and Kidney Disease Improving Global Outcomes (KDIGO) recommendations for patients with CKD.¹⁻¹⁰ The evidence for vitamin D analogs is limited due to lack of long-term data on clinically meaningful outcomes such as mortality, bone fracture rates, and cardiovascular outcomes. Surrogate endpoints such parathyroid hormone (PTH) levels are subject to large variations between assays which make comparisons between clinical trials difficult. Some results analyzed vitamin D analogs as either established agents (vitamin D, 24,25 hydroxyvitamin D₃, 1,25 dihydroxyvitamin D₃ [calcitriol] and 1 α -hydroxyvitamin D₃ [alfacalcidol]) or newer vitamin D compounds (doxercalciferol, paricalcitol, falecalcitriol and maxacalcitol). Afacalcidol, maxacalcitol and falecalcitriol are not available in the United States (US).
- Evidence for use of vitamin D analogs in children with CKD on growth rate, bone fracture rates, electrolyte changes and cardiovascular disease is insufficient.³
- Evidence for use of vitamin D analogs in adults with CKD to impact fracture rates, bone pain, parathyroidectomy, cardiovascular outcomes, and need for renal replacement therapy is insufficient. Comparative efficacy between the treatments is also insufficient.

- Low quality evidence from small, short-term studies suggest there is no mortality benefit for vitamin D analogs in patients with stage 2-4 CKD (RR 1.40; 95% CI, 0.38 to 5.15).¹ Mortality compared to placebo was not different for established vitamin D analogs (RR 1.49; 95% CI, 0.14 to 15.69) compared to newer vitamin D analogs (RR 1.09; 95% CI, 0.16 to 7.34). In patients on hemodialysis, no difference was observed between patients who received vitamin D analogs or placebo (117 deaths vs. 116 deaths, respectively (p=0.67) (based on low quality of evidence).²
- There is moderate quality evidence, based on 2 trials, that newer vitamin D analogs decrease PTH levels more than 30% from baseline in 87.5% of patients compared to 11% of patients on placebo who have CKD not requiring dialysis (RR 7.87; 95% CI 4.87 to 12.73).¹ There was insufficient evidence to compare this surrogate outcome with older, established vitamin D analogs.
- There is moderate quality evidence in patients requiring dialysis that vitamin D analogs decrease PTH levels more than 30% in 73% of patients compared to 10% in placebo-treated patients (RR 5.90; 95% CI, 3.17 to 10.96).² In a separate analysis between paricalcitol and placebo in patients undergoing hemodialysis, paricalcitol was found to decrease PTH levels more than 30% from baseline in 73% of patients receiving IV paricalcitol compared to 10% of placebo-treated patients (RR 6.37; 95% CI, 4.64 to 8.74; P<0.001).⁴ Low quality evidence found that in patients requiring dialysis, paricalcitol decreased PTH levels more than 30% from baseline in 61.1% of patients compared to 73.3% of calcitriol treated patients (p=0.29) based on one small randomized-controlled trial.⁵
- Extended-release (ER) calcifediol decreased PTH levels in 2 identical, double-blind, randomized, placebo-controlled, 26-week trials in patients (n= 429) with stage 3 or 4 CKD and secondary hyperparathyroidism. Low strength of evidence found ER calcifediol to reduce PTH levels by 30% or more from baseline in 33% of patients compared to 8% in the placebo group in the first study (Study A) and by 34% and 7%, respectively, in the second study (Study B) (NNT=4 for both studies).⁶
- There is low quality evidence that paricalcitol decreases proteinuria (RR 1.68; 95% CI, 1.25 to 2.25; P<0.001).⁵
- There is moderate quality evidence to not recommend routinely prescribing vitamin D analogs to patients with CKD unless there is evidence of vitamin D deficiency or PTH suppression.⁷
- Common harms associated with vitamin D analogs are disturbances in calcium and phosphate levels. Patients with CKD on dialysis and patients with CKD not on dialysis were analyzed separately. There is moderate quality evidence that use of vitamin D analogs result in a statistically significant higher incidence of hypercalcemia than placebo in patients with CKD not requiring dialysis (5.2% vs. 3.9%, respectively; p=0.022)¹ In patients requiring dialysis, established vitamin D analogs had a 31% incidence of hypercalcemia compared to 10% in placebo-treated patients (p=0.26) and newer vitamin D analogs had a 43% risk compared to 0% risk with placebo (p=0.020).¹
- There is low quality evidence that there was not a meaningful clinical difference between vitamin D analogs and placebo in risk of hyperphosphatemia.²
- In comparisons in patients requiring dialysis, there was low strength of evidence of no difference for risk of hypercalcemia or hyperphosphatemia between vitamin D analogs.

Recommendations:

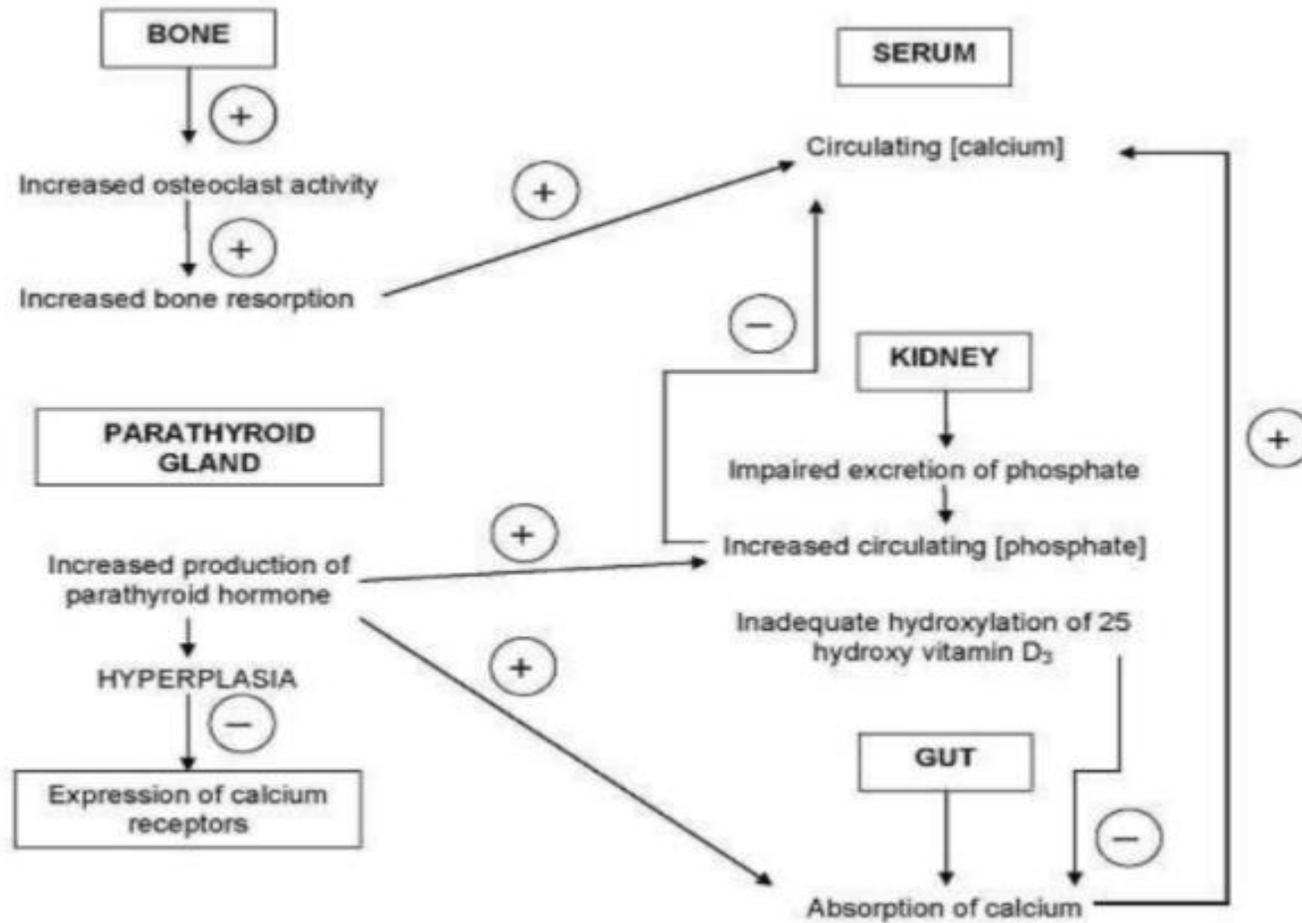
- Add a PDL class for Vitamin D analogs on the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription drug plan.
- There is no evidence to suggest that newer vitamin D analogs are more effective or associated with less harm than the preferred agent calcitriol. Recommend to continue to keep calcitriol as the only preferred vitamin D analog and designate paricalcitol, doxercalciferol and calcifediol non-preferred.

Background:

Mineral metabolism can be altered in patients with CKD (Figure 1).¹ Altered mineral metabolism can manifest as elevated phosphorous levels, low serum calcium, low vitamin D levels and increased PTH levels. Abnormalities result from reduced vitamin D formation due to insufficiency of kidney function.¹ Vitamin D is necessary for the absorption of calcium and maintenance of calcium homeostasis. Low vitamin D levels cause hypocalcemia that results in stimulation of the parathyroid gland. Abnormal stimulation of the parathyroid gland causes elevated PTH levels leading to secondary hyperparathyroidism (SHPT). Additionally, bone turnover can be accelerated to compensate for low calcium levels and result in compromised bone integrity.⁸ Impaired kidney function also leads to decreased excretion of phosphate which potentiates hypocalcemia due to precipitation of phosphorous with calcium in the tissues.¹ The mineral imbalances associated with CKD are called chronic kidney disease mineral-bone disorder (CKD-MBD).⁸

Elevated calcium and phosphorous levels are associated with increased morbidity and mortality demonstrating the importance of normalizing calcium and phosphorous levels.⁹ Abnormal bone turnover, tissue mineralization (calcium deposits in tissue), growth in children, arterial, valvular and myocardial calcification and other soft tissue calcification may result from hypocalcemia and hyperphosphatemia.¹⁰ Elevated PTH levels have been linked to increased risk of mortality in patients with CKD based on observational data.¹ The National Kidney Foundation recommends supplementation with ergocalciferol and cholecalciferol to correct disturbances when there is suspected or documented vitamin D deficiency in patients with CKD.⁷ When ergocalciferol or cholecalciferol fail to correct PTH levels then vitamin D analogs are initiated.⁶ Vitamin D analogs suppress PTH secretion and are thought to be more selective and less likely to cause hypercalcemia and hypophosphatemia than ergocalciferol and cholecalciferol. Hypercalcemia and hyperphosphatemia limit the use and doses of vitamin D analogs because these conditions are associated with increased adverse cardiovascular events and mortality.^{2,9} Contraindications to vitamin D analogs include phosphorous concentrations greater than 5.5 mg/dL and serum hypercalcemia (>9.5 mg/dL) due to their associated increase risk for metastatic and vascular calcification.^{1,2}

Figure 1. Mineral metabolism in chronic kidney disease



Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2009;(4):CD008175 doi:10.1002/14651858.CD008175.

Four vitamin D analogs have been approved by the U.S. Food and Drug Administration (FDA): calcifediol, calcitriol, doxercalciferol, and paricalcitol (Table 1).¹¹⁻¹⁴ Studies have shown the oral and intravenous (IV) formulations of calcitriol similarly suppress PTH and result in similar adverse events. Adynamic bone disease, abnormally low bone turnover, may also occur if vitamin D analogs are used when PTH levels are less than 150 pg/mL and are therefore not recommended.

Table 1. Indications and Dosing¹²⁻¹⁵

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Calcitriol	<ul style="list-style-type: none"> - Secondary hyperparathyroidism in patients with moderate to severe CKD (CrCl 15 to 55 mL/min) not on dialysis - Hypocalcemia/metabolic bone disease in patients undergoing chronic renal dialysis - Hypocalcemia in hypoparathyroidism/pseudohypoparathyroidism 	0.25 mcg or 0.5 mcg oral capsules 1 mcg/mL oral solution	Initiate at the lowest dose; titrate dose according to twice weekly serum calcium levels. Obtain serum calcium levels once monthly when on maintenance therapy. Hypocalcemia (dialysis): initiate at 0.25 mcg/day; increased by 0.25 mcg/day every 4 to 8 weeks if needed Hypocalcemia (pre-dialysis): initiate at 0.25 mcg/day; may increase to 0.5 mcg/day if needed (0.01-0.015 mcg/kg/day in pediatric patients age <3 years) Hypoparathyroidism: initiate at 0.25 mcg/day; titrate every 2 to 4 weeks if needed
Calcifediol	<ul style="list-style-type: none"> - Secondary hyperparathyroidism in adults with stage 3 or 4 CKD and serum total 25-hydroxyvitamin D levels less than 30 ng/mL - Not for patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis 	30 mg ER oral capsules	30 mcg once daily; may increase to 60 mcg once daily after 3 months if needed.
Doxercalciferol	<ul style="list-style-type: none"> - IV: secondary hyperparathyroidism in patients with CKD on dialysis - Oral: secondary hyperparathyroidism in patients with Stage 3 or 4 CKD 	2 mcg and 4 mcg IV sol 1 mcg and 2 mcg oral capsules	IV: 4 mcg TIW at the end of dialysis. Dose may be increased at 8-week intervals by 1-2 mcg Oral: Dialysis patients: 10 mcg TIW; may increase by 2.5 mcg at 8-week intervals if needed (max dose of 60 mcg/week) Pre-dialysis: 1 mcg/day; may increase by 0.5 mcg at 2-week intervals if needed (max dose of 3.5 mcg/day)
Paricalcitol	<ul style="list-style-type: none"> - IV: secondary hyperparathyroidism associated CKD on dialysis - Oral capsules: secondary hyperparathyroidism associated with stage 3 or 4 CKD 	0.04 mcg/kg to 0.1 mcg/kg IV sol 1 mcg, 2 mcg, and 4 mcg oral capsules	IV: given as a bolus dose no more frequently than every other day during dialysis; may increase by 2-4 mcg at 2 or 4 week intervals if needed Oral: 1 or 2 mcg once daily or TIW, dependent on baseline iPTH levels; may increase every 2 or 4 weeks if needed

Abbreviations: CKD = chronic kidney disease; CrCl = creatinine clearance; ER = extended-release; iPTH = intact parathyroid hormone; IV = intravenous; TIW = three times weekly

Parathyroid hormone levels are often used to monitor therapeutic efficacy of vitamin D analogs; however, because inactive and active fragments are measured, assays often have large variations.³ Levels of intact parathyroid hormone (iPTH) in dialysis patients should be between 150 and 300 pg/mL. However, clinically meaningful outcomes for treatment of vitamin D analogs include reduced risk for bone fractures, bone pain, muscle weakness, need for renal replacement therapy or dialysis, parathyroidectomy, cardiovascular disease, and mortality. Patients who receive vitamin D analogs should be monitored for adverse effects, which include hyperphosphatemia and hypercalcemia. Serum phosphorous levels of 3.5 to 5.5 mg/dL and serum corrected total calcium levels of 8.4 to 9.5 mg/dL are recommended and should be routinely monitored.¹

Calcitriol is currently the most utilized vitamin D analog in the OHP fee-for-service population.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane Collaboration – Vitamin D Compounds and Chronic Kidney Disease Pre-Dialysis

In 2009, the Cochrane Collaboration systematically reviewed evidence for the use of vitamin D compounds and suppression of PTH in patients with CKD not on dialysis.¹ Studies included in the review were randomized controlled trials (RCTs) using vitamin D analogs to manage CKD mineral and bone disorder in patients with CKD not requiring dialysis. Several vitamin D analogs were included in the review but the only agents approved by the FDA used in this review were calcitriol (5 studies), doxercalciferol (1 study), and paricalcitol (1 study). Sixteen RCTs of oral or IV formulations met inclusion criteria. Ten studies were placebo-controlled. Most studies were small (less than 50 participants) with a duration of less than 12 months. All patients had CKD: 2 studies with stage 2 or lower, 8 studies enrolled stage 3 or lower, and 3 studies enrolled stage 4 or lower. The overall quality of most of the studies was poor.

Vitamin D compounds did not reduce mortality (RR 1.40; 95% CI, 0.38 to 5.15) or prevent need for dialysis during the studies (RR 0.76; 95% CI, 0.36 to 1.62).¹ However, vitamin D compounds reduced PTH levels compared to placebo by a mean difference (MD) of -49.34 pg/mL (95% CI, -85.70 to 12.97 pg/mL), based on 4 studies. Vitamin D compounds were also associated with higher phosphorous levels compared to placebo by a MD of 0.37 mg/dL (95% CI, 0.09 to 0.66 mg/dL) and increased serum calcium by a MD of 0.20 mg/dL (95% CI, 0.17 to 0.23 mg/dL). Evidence for reduction in bone fractures, parathyroidectomy and bone pain was insufficient to draw conclusions. Of the 9 studies which reported harms, one study found nausea and vomiting with paricalcitol to be similar to placebo.

There was insufficient comparative evidence between calcitriol and newer vitamin D analogs. Limitations to the analysis included small study sizes so there was likely insufficient power to detect differences in meaningful outcomes (e.g., mortality and morbidity outcomes) between treatments if they do exist.

Cochrane Collaboration – Vitamin D Compounds and Chronic Kidney Disease in Patients Requiring Dialysis

A second systematic review was performed to determine the role of vitamin D compounds in patients with CKD requiring dialysis.² The effect of vitamin D compounds on mortality, PTH and bone tissue was investigated. To be included in the review trials had to be RCTS of vitamin D compounds used to manage CKD mineral and bone disorders in patients with CKD and undergoing dialysis. Sixty studies met the inclusion criteria. Among the vitamin D analogs included in the review, calcitriol (7 studies), doxercalciferol (1 study) and paricalcitol (6 studies) were the only agents approved by the FDA. Thirteen studies were head-to-head studies; however, only 2 of these studies evaluated drugs available in the U.S. (n=294). Most studies enrolled less than 75 participants. Pediatric patients were represented in 6 studies. Most studies (n=50) enrolled patients on hemodialysis and 7 studies included patients with peritoneal dialysis. Most studies were deemed to be poor quality.

Meta-analysis was limited due to heterogeneity of study outcomes. No difference in mortality was found between vitamin D analogs and placebo (RR 1.34; 95% CI, 0.34 to 5.24).² Rates of bone fracture, bone pain, and effects on stature were similar between vitamin D analogs and placebo; however, the number of outcomes were too low to draw meaningful conclusions. Vitamin D analogs lowered PTH levels but assessment of differences in efficacy between vitamin D analogs was limited. One study found newer analogs similarly lowered PTH levels as older vitamin D analogs (MD 19.0 pg/mL; 95% CI, -96.2 to 134.2 pg/mL). Eight additional studies reported PTH levels but were not reported in a way that allowed for meta-analysis. Placebo-controlled studies found vitamin D analogs lowered PTH levels more than placebo by a MD of -196.05 pg/mL; 95% CI, -298.43 to -93.66 pg/mL). Suppression of PTH levels by 30% or more was accomplished more effectively with vitamin D analogs than placebo (RR 5.90; 95% CI, 3.17 to 10.96). Both newer and established vitamin D analogs suppressed PTH levels by 30% or more by similar extent compared to placebo (RR 2.72; 95% CI, 1.12 to 6.61 and RR 7.05; 95% CI, 3.82 to 13.04, respectively).

Serum phosphorous levels were significantly increased with vitamin D analogs, compared to placebo in data from 2 studies (MD 0.70 mg/dL; 95% CI, 0.08 to 1.33) and hypercalcemia was more common with vitamin D analogs compared to placebo (39% vs. 5%; p = 0.070).² Newer vitamin D analogs were associated with a higher incidence of hypercalcemia compared to placebo but serum phosphorous data were not reported. Evidence suggests that IV vitamin D analogs may suppress PTH more than oral formulations but evidence is insufficient to draw strong conclusions. There was insufficient evidence on the effect of different dosing strategies on outcomes.

In head-to-head comparisons of vitamin D analogs, no difference in mortality was found based on data from 94 patients.² There was insufficient evidence to draw conclusions on bone fracture rates and bone pain. One study of PTH levels found no difference between the newer vitamin D analogs on PTH suppression. Phosphorous levels were also similar between agents. One study found serum calcium levels to be similar between older and newer vitamin D analogs (MD 0.30 mg/dL; 95% CI, -0.11 to 0.71 mg/dL).

Cochrane Collaboration – Interventions for Metabolic Bone Disease in Children with Chronic Kidney Disease

A 2015 systematic review assessed the role of interventions for metabolic bone disease in children with Stage 2 to Stage 5 CKD (including patients on dialysis).³ Randomized trials evaluating CKD-MBD (stages 2-5, including dialysis patients) in children and adolescents (up to age 21) were included. Eighteen studies were identified (n=576) of children up to the age of 21 years. Interventions included in the studies included dietary interventions, vitamin D compounds and analogs, calcimimetic agents and phosphate-binding agents.

Change in PTH levels was the most commonly investigated outcome with little evidence on growth or bone deformities. Most of the studies had high risk of performance bias. Two studies compared oral versus intraperitoneal calcitriol. One study was too small to draw meaningful conclusions (n=7) and the second found no difference between the types of administration for the outcomes of suppression of PTH, hyperphosphatemia, hypercalcemia or bone histology. Intermittent compared to once daily dosing of calcitriol was evaluated in 3 studies (n=104).³ PTH levels, height, hypercalcemia and hyperphosphatemia were not statistically different between groups. Six studies compared vitamin D analogs. In placebo-controlled comparisons, IV formulations of calcitriol and paricalcitol were more effective at lowering PTH levels without differences in risk of hypercalcemia. One head-to-head found no significant differences in parameters of bone health when doxercalciferol was compared to calcitriol, on background sevelamer or calcium carbonate. Limitations to this review include the insufficient evidence available on growth rates, bone fracture rates, or cardiovascular calcification. Additionally, many studies were too small to detect a treatment difference if differences in these outcomes did exist.

Paricalcitol Use in Chronic Kidney Disease

The efficacy and safety of paricalcitol was evaluated in a systematic review and meta-analysis of RCTs in patients with Stage 2-5 CKD.⁴ The analysis included RCTs of patients with stage 2-5 CKD and any dose or type (oral or IV) of paricalcitol. The Jadad scale score (0-5) and risk of bias were assessed to evaluate the quality of the included trials. Efficacy outcomes studied were proteinuria, PTH suppression, and serum calcium and phosphorous levels. Nine placebo-controlled trials were included (n=832). The majority of studies were of good quality with a Jadad score of greater than 3. Five trials were in patients on hemodialysis and 4 trials were in patients with stage 2-4 CKD. Durations of trials ranged from 4 weeks to 6 months. The primary outcomes were either changes in intact PTH levels, incidence of proteinuria or changes in urine albumin/creatinine ratio.

Four studies (n=469) evaluated the effect of oral paricalcitol compared to placebo on reducing residual albuminuria in patients with CKD on background angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Use of oral paricalcitol 1-2 mcg/day statistically significantly reduced proteinuria (defined as $\geq 10\%$ reduction in proteinuria) versus placebo (RR 1.68; 95% CI, 1.25 to 2.25; $p < 0.001$).⁴ Paricalcitol decreased PTH levels at least 30% from baseline more than placebo (RR 6.37; 95% CI, 4.64 to 8.74; $p < 0.001$) based on 5 trials (n=563). Fifty-six percent of patients were receiving IV paricalcitol and undergoing hemodialysis and 44% were taking oral paricalcitol and had CKD stage 3 and 4. Hypercalcemia was not significantly more common with paricalcitol compared to placebo (RR 2.25; 95% CI, 0.81 to 6.26; $p = 0.12$). Phosphorous levels were only reported in one trial, so meta-analysis was not performed. Risk of harms were reported in 6 trials. Adverse events were not statistically significantly different between paricalcitol and placebo (58 vs. 28; RR 1.28; 95% CI, 0.84 to 1.94; $P = 0.26$). Limitations of the meta-analysis include heterogeneity of the data, such as different primary endpoints studied, use of oral and IV paricalcitol, and lack of evidence on long-term outcomes, such as progression of renal disease, bone fracture rates and mortality.

Clinical Practice Guidelines:

Kidney Disease: Improving Global Outcomes (KDIGO)

In 2012 the KDIGO published their updated recommendations for the management, evaluation and treatment of patients with CKD.⁷ The GRADE system was used to evaluate the literature and assign strength of recommendations to the quality of evidence. In addition to the quality of the recommendation, the committee assigned a grade of level 1 or level 2 depending on the evidence. Level 1 evidence was defined as “most patients should receive the recommended course of action” or level 2 defined as “different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences”. A Guidance pertaining to use of vitamin D analogs will be presented here. All patients with CKD and an estimated glomerular filtration rate (GFR) of less than 45 mL/min/1.73 m² should have serum calcium, phosphate, PTH and alkaline phosphatase levels evaluated based on low quality evidence. Patients with elevated PTH levels should also be tested for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. The

KDIGO do not recommend routinely adding vitamin D supplements or vitamin D analogs in patients with CKD and not on dialysis without documentation of vitamin D deficiency or elevated PTH levels based on level 2 moderate quality of evidence.

National Institute for Health and Care Excellence (NICE)

Recommendations for management of adults with CKD were updated by NICE in 2014.¹⁵ Recommendations related to CKD and treatment with vitamin D analogs include measurement of calcium, phosphorous, PTH and vitamin D levels should be performed only in patients with a GFR less than 30 mL/min/1.73 m². Routine vitamin D supplementation should not be used to manage CKD-mineral and bone disorders. Cholecalciferol or ergocalciferol supplements are recommended to treat vitamin D deficiency in CKD; however, if symptoms of CKD-mineral and bone disorders persist after correction of vitamin D deficiency, alfacalcidol (not available in the US) or calcitriol are recommended to patients with a GFR less than 30 mL/min/1.73 m². Serum phosphate and calcium levels should be routinely monitored in patients receiving vitamin D supplements or analogs.

Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care

An update of the 2007 VA/DoD guideline on the management of CKD in primary care was published in 2014.¹⁶ Clinical management strategies pertaining to the use of vitamin D analogs include a weak recommendation to not have primary care physicians prescribe vitamin D analogs in patients with Stage 3 and 4 CKD with elevated PTH levels. This recommendation is based on the lack of evidence of kidney, bone or cardiovascular benefit for broad use. Referral to a nephrologist is recommended for management of vitamin D analogs.

Randomized Controlled Trials:

There are a limited number of high quality RCTs evaluating vitamin D analogs. Comparative studies of effectiveness between the different vitamin D compounds are of interest and available evidence is presented below in Table 2.

Table 2. Summary of Direct Comparative Studies Completed

Study	Comparison	Population	Primary Outcome	Results
Coyne, et al ¹⁷ PG, RCT, MC, OL 24 weeks	paricalcitol 1 mcg/day* vs. calcitriol 0.25 mcg/day*	Patients with Stage 3-4 CKD and secondary hyperparathyroidism N= 110	Hypercalcemia \geq 10.5 mg/dL	Paricalcitol: 3 (6%) calcitriol: 1 (2%) p =0.36
Ong, et al ⁵ PG, RCT, OL 24 weeks	oral paricalcitol daily † vs. oral calcitriol daily † † Dose based on iPTH levels and titrated every 3 weeks to obtain an iPTH level of 150-300 pg/mL	Patients with secondary hyperthyroidism on dialysis N=66	\geq 30% reduction in iPTH	paricalcitol: 22 (61.1%) calcitriol: 22 (73.3%) p =0.29

Abbreviations: CKD = chronic kidney disease; iPTH = intact parathyroid hormone; MC = multi-center; OL = open-label; PG = parallel group; RCT = randomized controlled trial
* Initial dose

NEW DRUG EVALUATION

Clinical Efficacy:

Extended-release calcifediol was studied in 2 identical placebo-controlled, double-blind, Phase 3 RCTs in a total of 429 patients with stage 3 or 4 CKD and secondary hyperparathyroidism.⁶ Patients were randomized to ER calcifediol 30 or 60 mcg daily at bedtime or placebo. The mean age of patients was 66 years with a mean iPTH level of 147.2 pg/mL. The primary outcome was a 30% or greater reduction in PTH level from baseline at 26 weeks. Secondary outcomes were incidence of hypercalcemia, defined as 2 consecutive serum calcium values of more than 10.3 mg/dL, and hyperphosphatemia, defined as 2 consecutive serum phosphorous levels more than 5.5 mg/dL. Secondary outcomes had to be deemed to be related to the study drug, which may introduce bias since hypercalcemia and hyperphosphatemia are known adverse effects of vitamin D analogs. The first trial found PTH levels reduced by more than 30% in 33% of patients taking ER calcifediol compared to 8% taking placebo (p<0.001, CI not provided; NNT 4 over 26 weeks) (Table 4). The second study found 34% of patients in the ER calcifediol group and 7% in the placebo group obtained the primary endpoint (p<0.001, CI not provided; NNT 4)(Table 4).⁶ Lack of details on study methodology limit the strength of evidence of these findings and suggest the potential for high risk of bias. Long-term studies of health outcomes (i.e., mortality, bone fracture rates, parathyroidectomy, etc.) would be more helpful to determine the benefit of ER calcifediol.

Clinical Safety:

At total of 5.7% of patients in the ER calcifediol group discontinued the first trial early due to adverse events compared to 2.8% in the placebo group.⁶ In the second study, discontinuation rates due to adverse events were 4.9% in the ER calcifediol group and 5.6% in the placebo group.⁶ Adverse events occurring more commonly with ER calcifediol compared to placebo are presented in Table 3. Six patients who received ER calcifediol experienced hypercalcemia compared to none in the placebo groups based on a pooled data analysis of both studies. The incidence of hyperphosphatemia was 0.4% in the ER calcifediol groups compared to 0% in the placebo group based on pooled data.

Table 3. Adverse Events Occurring in \geq 1.4% of Patients Treated with ER Calcifediol Compared to Placebo¹¹

Adverse Reaction	Placebo (n=144)	ER Calcifediol (n=285)
Anemia	3.5%	4.9%
Nasopharyngitis	2.8%	4.9%
Blood creatinine increase	1.4%	4.9%
Dyspnea	2.8%	4.2%
Cough	2.1%	3.5%

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Mortality
- 2) Bone fractures
- 3) Requirement for dialysis
- 4) Reduction in PTH

Primary Study Endpoint:

- 1) Reduction in PTH

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Sprague, et al. ⁶ RCT, DB, PC, MC 26 weeks	1. ER Calcifediol 30 or 60 mcg daily (C)* 2. Placebo daily (P) ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels	<u>Demographics:</u> Age: 65 years Male: 52% White: 63% eGFR: 31 mL/min/1.73 m ² iPTH: 144.5 pg/mL 25-hydroxyvitamin D: 19.7 ng/dL <u>Key Inclusion Criteria:</u> - iPTH >70 pg/mL - 25-hydroxyvitamin D <30 ng/mL - Stage 3-4 CKD - Age ≥18 years - eGFR ≥15 to <60 ml/min/1.73 m ² - 25-hydroxyvitamin D ≥ 10 ng/dL - plasma iPTH ≥ 85 and < 500 pg/ml - Serum Ca ≥8.4 to <9.8 mg/dL - P ≥2.0 to <5.0 mg/dL <u>Key Exclusion Criteria:</u> - Ca:SCr ratio >0.2 - Nephrotic proteinuria (SCr >3 mg/mL) - Parathyroidectomy for SHPT - Renal transplant - Dialysis - Bone metabolism therapy	<u>ITT:</u> C: 141 P: 72 <u>Attrition:</u> C: NR P: NR	<u>Primary Endpoint:</u> Reduction in iPTH ≥30%: C: 47 (33%) P: 8 (8%) (CI not provided) p<0.001 <u>Secondary Endpoints:</u>	25%/4	Hypercalcemia*: C: 6 (2%) P: 0 (0%) p-value NR Hyperphosphatemia* : C: 1 (0.4%) P: 0 (0%) p-value NR Discontinuations due to AE: C: 8 (5.7%) P: 2 (2.8%) p-value NR Anemia*: C: 7 (4.9%) P: 3 (3.5%) p-value NR Increased SCr*: C: 7 (4.9%) P: 1 (1.4%) p-value NR * Only pooled data from Study A and B was reported	NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (unclear) randomized 2:1, process not described. <u>Performance Bias:</u> (low) blinding of subjects and staff described and maintained allocation concealment. <u>Detection Bias:</u> (unclear) details on outcome assessment was not provided. <u>Attrition Bias:</u> (unclear) 17% of patients from both studies discontinued but details were not provided. True ITT analysis was used and dropouts were categorized as non-responders. <u>Reporting Bias:</u> (unclear) Pre-specified outcomes reported. Study funded by manufacturer. Applicability: <u>Patient:</u> Patients are representative of those requiring vitamin D analogs and not requiring dialysis. <u>Intervention:</u> Labeled doses of 30 to 60 mcg daily administered. <u>Comparator:</u> Placebo comparison appropriate to establish efficacy. <u>Outcomes:</u> pre-specified surrogate outcomes measured. Outcomes such as mortality, need for renal replacement therapy and fractures would help to better inform treatment decisions. <u>Setting:</u> Eighty-nine US sites (both studies).

<p>2. Sprague, et al.⁶</p> <p>RCT, DB, PC, MC</p> <p>26 weeks</p>	<p>1. ER Calcifediol 30 or 60 mcg daily (C)*</p> <p>2. Placebo daily (P)</p> <p>ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels</p>	<p><u>Demographics:</u> Age: 66 years Male: 48% White: 66% eGFR: 31 mL/min/1.73 m² iPTH: 151.6 pg/mL 25-Hydroxyvitamin D: 19.6 ng/dL</p> <p><u>Key Inclusion Criteria:</u> See above</p> <p><u>Key Exclusion Criteria:</u> See above</p>	<p><u>ITT:</u> C: 144 P: 72</p> <p><u>Attrition:</u> C: NR P: NR</p>	<p><u>Primary Endpoint:</u> Reduction in iPTH levels by at least 30%: C: 49 (34%) P: 5 (7%) (CI not reported) p<0.001</p> <p><u>Secondary Endpoints:</u></p>	<p>27%/4</p>	<p>See above</p>	<p>Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (unclear) see above. <u>Performance Bias:</u> (low) see above. <u>Detection Bias:</u> (unclear) see above. <u>Attrition Bias:</u> (unclear) see above. <u>Reporting Bias:</u> (unclear) see above.</p> <p>Applicability: <u>Patient:</u> see above. <u>Intervention:</u> see above. <u>Comparator:</u> see above. <u>Outcomes:</u> <u>Outcomes:</u> see above. <u>Setting:</u> see above.</p>
<p><u>Abbreviations</u> [alphabetical order]: ARR = absolute risk reduction; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone ITT = intention to treat; MC – multi-center; mITT = modified intention to treat; MR = modified release; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; P = phosphorous; PP = per protocol; SCr = serum creatinine; SHPT = secondary hyperparathyroidism.</p>							

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Appendix 1: Specific Drug Information

Table 5. Clinical Pharmacology and Pharmacokinetics

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Calcitriol (Rocaltrol®)	Synthetic vitamin D analog which regulates absorption of calcium from the GI tract and utilization throughout the body.	Rapidly absorbed from the intestine	<ul style="list-style-type: none"> • 24-hydroxylase and hydroxylation • enterohepatic recycling and biliary excretion 	<ul style="list-style-type: none"> • Half-life: 5-8 hours • Cmax: not provided • AUC: 60 pg/mL at 2 • Vd: not provided • 99% protein bound
Doxercalciferol (Hectoral®)	Synthetic vitamin D analog that undergoes activation to the biologically active form of vitamin D2.	Rapidly absorbed from the intestine	<ul style="list-style-type: none"> • Metabolized by CYP27 in the liver and by hydroxylation in the kidney 	<ul style="list-style-type: none"> • Half-life: 32-37 hours • Cmax: at 11-12 hours (levels not provided) • AUC: 60 pg/mL • Vd: not provided
Paricalcitol (Zemplar®)	Synthetic vitamin D2 analog of calcitriol resulting in reduced PTH synthesis and secretion.	72-86%	<ul style="list-style-type: none"> • Metabolized by CYP24, CYP3A4 and UGT1A4 • Excreted in the feces 	<ul style="list-style-type: none"> • Half-life: 4-6 hours • Cmax: not provided • AUC: not provided • Vd: 34 L • >98% protein bound
Calcifediol (Rayaldee®)	Converted to calcitriol in the kidney resulting in increased intestinal absorption of calcium and phosphorous and decreased PTH synthesis.	Increased absorption with high fat, high calorie meal	<ul style="list-style-type: none"> • Metabolized by CYP450 primarily in the kidney • Excreted by fecal and biliary route 	<ul style="list-style-type: none"> • Half-life: 11 days • Cmax: not provided • AUC: not provided • Vd: 8.8. L • >98% protein bound

Use in Specific Populations:

Calcitriol: use in patients with renal insufficiency (nephrotic syndrome and undergoing dialysis) were found to have lower pre-dose and peak calcitriol levels with at least double the half-life compared to normal subjects. No specific dosing recommendations were provided.

Calcifediol: use in pediatric patients has not been studied.

Doxercalciferol: use in pediatric patients has not been studied. Use with caution in patients with impaired hepatic function.

Paricalcitol: not recommended to be used during breast feeding.

Drug Safety:

FDA Boxed Warnings:

There are no FDA boxed warnings for vitamin D analogs.

Contraindications:

Author: Sentena

Date: January 2017

Calcifediol: none

Calcitriol, doxercalciferol and paricalcitol: do not use in patients with hypercalcemia or evidence of vitamin D toxicity.

Table 6. Summary of Warnings and Precautions

Warning/Precaution	Calcitriol	Doxercalciferol	Paricalcitol	Calcifediol
Hypercalcemia	X	X	X	X
Hyperphosphatemia		X		
Adynamic bone disease				X
Digitalis toxicity			X	X
Increased serum creatinine	X			
Over-suppression of PTH		x		
Aluminum overload			X	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to November Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Calcitriol/	7143	
2	paricalcitol.mp.	478	
3	calcifediol.mp. or Calcifediol/	1918	
4	doxercalciferol.mp.	79	
5	1 or 2 or 3 or 4	9039	
6	limit 5 to (english language and humans)	6488	
7	limit 6 to (clinical trial, all or clinical trial or comparative study or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	1561	
8	limit 7 to yr="2007 -Current"	739	