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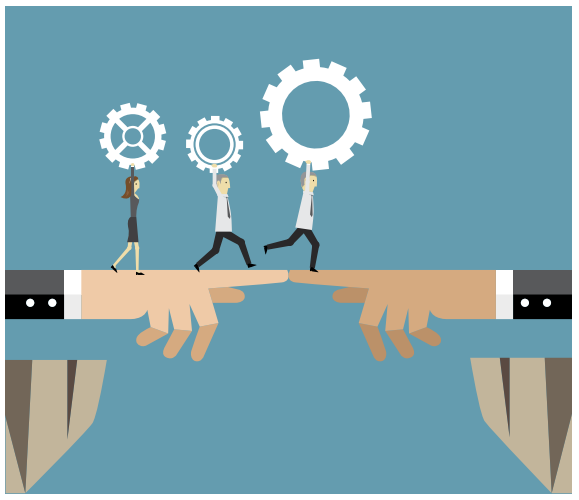
Business Shifts Likely to Shape Future of Nephrology

By Bridget M. Kuehn



The merger between pharmacy giant CVS and health insurer Aetna is among the latest shake-ups in the healthcare industry that are likely to have ripple effects on nephrologists and patients with kidney diseases. The merger was finalized on November 28, 2018.

For nephrologist Bruce Culleton, MD, vice president of CVS Health, the CVS-Aetna merger offers the prospect of a new care delivery model that better meets patients' needs.

"We believe this type of consolidation encourages the development of business models that are more patient-centric and more holistic than the current paradigm, which is focused on in-center dialysis care," Culleton said. "Future models will support chronic kidney disease identification and care, dialysis options education with an emphasis on access to transplantation and home dialysis, and innovation to deliver improved outcomes at lower overall healthcare costs."

Other experts in nephrology are cautiously optimistic that the merger could lead to new models of care and possibly better care for chronic diseases like hypertension that lead to kidney disease. But they also acknowledge that it is difficult to predict how this unusual merger might affect competition, costs, and quality. Most research to date on consolidation in healthcare has focused on mergers between care providers like hospitals or dialysis providers, which have mixed effects on care quality, access, and cost.

"The economics are less clear about what [the CVS-Aetna merger] will do to things like prices and potentially quality of care, compared to what sort of economic theory predicts about mergers and consolidations among the same types of organizations like among dialysis providers," said nephrologist Kevin Erickson, MD, MS, assistant professor of medicine at Baylor College of Medicine in Houston.

Seismic shifts

The Aetna-CVS merger will bring together a large national insurance company with a powerhouse in the pharmacy and retail clinic space. The goal, according to a statement from CVS Health President and Chief Executive Officer Larry J. Mello, is to create a better experience for healthcare consumers by merging Aetna's data and analytics with CVS frontline care.

It's also a move to protect CVS's mail order and pharmacy business lines, noted Janis Orlowski, MD, chief health care officer of the Association of American Medical Colleges. She explained that pharmaceutical manufac-

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Debate Rages on About Role of Obesity in Transplant Outcomes

By Bridget M. Kuehn

Obesity should not disqualify patients from kidney transplants, suggested one study presented at Kidney Week 2018, while two other studies provided conflicting information on whether pretransplant weight loss may be beneficial.

The prevalence of obesity in both adult and child prospective kidney transplant recipients has increased, mirroring a trend in the general population.

Observational studies have found that higher body mass index (BMI) is associated with an increased risk of delayed graft function, noted Krista Lentine, MD, professor of internal medicine at Saint Louis University School of Medicine, and colleagues, "but [higher BMI] is often *not* associated with inferior long-term allograft or patient survival in these studies." There are, however, increased risks of performing transplantation on patients who are obese compared to normal weight patients, including more surgical site complications, and there is some evidence of increased cardiovascular complications, noted Lentine, who has published a review on the topic.

"The debate regarding the impact of obesity on out-

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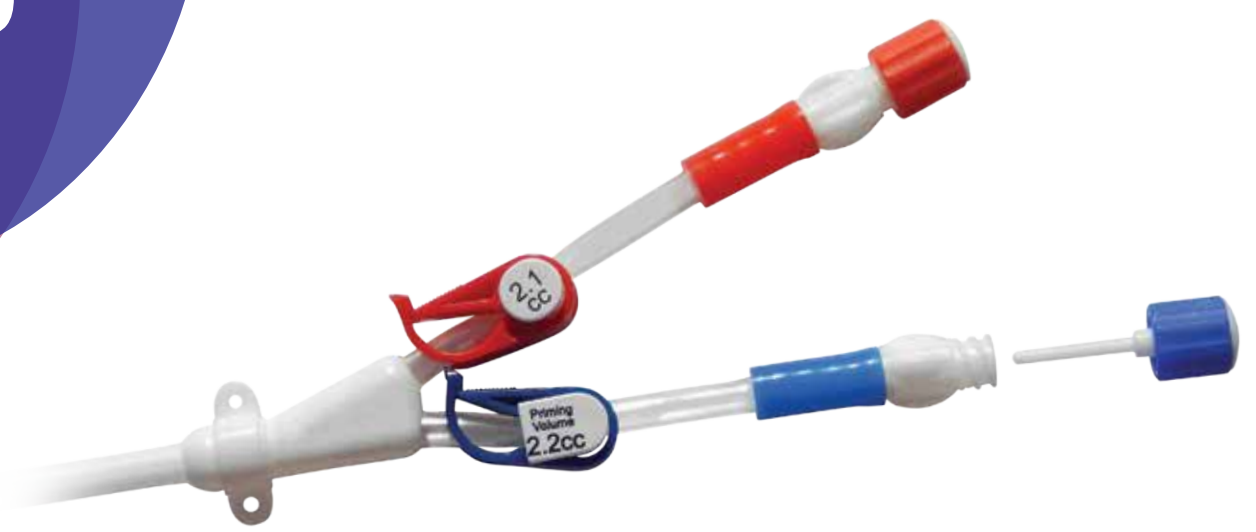

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[1]Brunelli, SM et al. 2018. J Am Soc Nephrol. Apr;29(4):1336-1343. [2]Hymes, JL et al. 2017. Am J Kidney Dis. Feb;69(2):220-227.

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Business Shifts

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turers have been increasingly trying to cut out the middleman in pharmaceutical sales. Additionally, newcomers like online commerce giant Amazon recently launched a home health division that could cut into CVS's sales of over-the-counter products like aspirin or vitamins. Orlowski predicted that merging with Aetna would allow CVS to capture Aetna's customers and prevent them from turning to Amazon or other competitors.

"It puts CVS clearly back in that middle because you get your insurance from them, so that's where you're going to get your drugs from," Orlowski said.

It will also give the two companies opportunities to disrupt the pharmaceutical market by determining which drugs they will cover.

"We are going to continue to see disruption," Orlowski predicted.

Another pending merger between health insurer Cigna and pharmacy benefit manager Express Scripts also aims to leverage the companies' data to improve care outcomes and customer service, according to a company statement.

But not everyone is convinced of the potential benefits of these complex business arrangements. The American Medical Association asked the US Department of Justice (DOJ) to oppose the CVS-Aetna merger, saying it poses a threat to competition among pharmacy benefit managers, health insurers, retail pharmacies, Medicare Part D plans, and specialty pharmacies. California's Insurance Commissioner Dave Jones also prevailed on the DOJ to block the move citing the potential for increased prices and decreased quality of care.

"The proposed merger of CVS and Aetna will significantly reduce competition in the pharmacy benefit management and Medicare Part D markets, affecting millions of healthcare consumers throughout the country," Jones wrote in a statement.

Despite the opposition, the DOJ approved the merger in October with the condition that Aetna must divest from its Medicare Part D prescription drug plans.

New care models

Orlowski predicts that the merged company could offer lower cost insurance plans that will cover primary care, vaccinations, or other low intensity services at CVS clinics. This could lead to more frequent visits to control hypertension, diabetes, or even early stages of kidney disease, she suggested. But she doesn't anticipate they would take on more advanced kidney care or transplant. Those patients she believes would still be seen in more traditional settings. The new company might, however, have some influence on what drugs are available to patients with transplants who are insured by their plans.

The company could also leverage its huge store of patient data to improve the care its patients receive, for example, by boosting compliance with medications.

"A tremendous advantage that the insurers have, is that they have all kinds of information regarding patients, their drugs, whether they're compliant with their drugs," Orlowski said. "Even if they don't know the diagnosis, they know what drugs you're taking so they can guess at what your diagnosis is, and as far as healthcare planning, quite frankly, other health providers would really like to have that information."

Baylor's Erickson agreed that enhanced monitoring of chronic disease or improved compliance with medications could help patients with early kidney disease.

"If they're focusing on trying to make it easier to receive prescribed treatments and they succeed at that, I think this really could be something that's helpful for patients with kidney disease," he said.

But he noted that many patients with more advanced chronic kidney disease don't have commercial insurance or are uninsured, until they develop end stage renal disease (ESRD) and become eligible for Medicare's ESRD program.

"Hopefully, CVS would be able to expand some of these new programs that they're talking about into other populations, not just those who have Aetna insurance," Erickson said.

Another potential downside to the trove of data the newly merged company will have is that it might be vulnerable to data breaches that might put patient privacy at risk, Orlowski noted. She also cautioned that while improving care may be part of the company's mission, their data will also be used to improve their profit margin.

"There's a dual mission and you always have to worry about the conflict in that dual mission," she said.

A foray into home dialysis

Prior to the merger, CVS Health announced it was launching a kidney disease care initiative. The initiative will leverage the company's data to identify patients with CKD earlier, and make home dialysis easier with an experimental device for which the company plans to seek US Food and Drug Administration approval.

"CVS Health is uniquely positioned to build a solution that will enable us to identify and intervene earlier with patients to optimize the management of chronic kidney disease, while at the same time making home dialysis therapies a real option for many more patients," Culleton said.

Although it is not yet clear what the merged company's plans are regarding the kidney care initiative, the prospect of new models for early kidney care and better access to home dialysis was welcomed by some observers.

"I'm cautiously excited about these developments," Erickson said. "We need to find new and better ways to deliver care. We need to find ways to slow the progression of kidney disease to smooth patients' transitions to dialysis, to promote things like preemptive kidney transplantation and home dialysis modalities. We need to do better at coordinating care for patients who do have ESRD and I think there's a lot of room for innovative new approaches to achieving these goals."

He said he hoped the company would not focus strictly on dialysis, but instead work to improve upstream care that delays the onset of ESRD or the need for dialysis.

"It would be great if there was also a focus on trying to keep people from developing ESRD and needing dialysis," he said.

He also welcomed CVS's initiative as another potential option for home dialysis.

"Making it more available to patients, efforts to educate patients and make them aware of this option, would be beneficial and could help to get more patients on home dialysis, which I think would be a better choice for some patients," he said.

Orlowski said that nephrologists in general should revisit the option of home dialysis. She noted that in-center dialysis is predominant in the United States for both business and other technical reasons. But she noted that the machines are becoming smaller, easier to use, and more efficient.

"I think that nephrologists need to re-look at home dialysis and what our opportunities are there," she said.

She also urged the profession itself to look to develop better ways to deliver care and how best to do that under new alternative payment plans and bundles.

"We need to be working with our healthcare systems on how do we prevent the progression of kidney disease through much earlier management of these diseases," Orlowski said. "It shouldn't be only CVS, it should be the healthcare community that says, 'Let's stamp out 10% of chronic kidney disease by earlier management.'"

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Role of Obesity

Continued from page 1

comes before and after kidney transplantation, and implications for transplant candidacy, have been waging for decades," Lentine said. "Part of the uncertainty and difficulty resolving the debate relates to limitations of a BMI, which is a measure of overall body size, and not specific for adiposity, as well as the limitations of available data."

The studies presented at Kidney Week are likely to add fuel to the debate, though they are unlikely to resolve it.

"Registry analyses can be very useful for hypothesis generation, but are also potentially limited by selection bias and uncontrolled confounding due to the nature of the available data," Lentine said.

Cutoff conundrum

It's common for transplant centers to consider BMI in assessing prospective kidney transplant recipients and opt against transplant for patients with BMIs above a set threshold.

"The impact of recipient obesity on long-term outcomes for kidney transplantation is not clear," said Bhavna Chopra, MD, a nephrologist in the renal transplant program at Allegheny General Hospital in Pittsburgh.

To further assess the effects of BMI on transplant outcomes, Bhavna and her colleagues used United Network of Organ Sharing data to identify all cases between 2006 and 2016 where each of a deceased donor's kidneys were transplanted into a different recipient. They looked at 39,334 paired kidney recipients who shared a donor to assess the effects of BMI on outcomes. Recipients with BMIs between 18 and 25 had significantly lower risks of death-censored graft failure and graft failure compared with patients whose BMIs were above 35, but risk of death was similar between the groups. Recipients with BMIs between 25 and 30 had a lower risk of death-censored graft failure than individuals with BMIs 35 and up, but the two groups had similar rates of graft failure and death.

Bhavna suggested that the non-inferior outcomes among patients with BMIs above 35 may reflect careful pretransplant selection in this subgroup for those most likely to have a successful outcome. Or it could reflect a survival advantage similar to that seen in patients who are obese and on dialysis, she noted. Lentine agreed that patient selection could have an impact on the outcome of an observational study.

"[Patients with obesity] who are selected for listing and ultimate transplantation are inherently healthier than the full population of [patients with obesity] with kidney failure," she said.

Based on the data, Bhavna suggested kidney transplantation BMI cutoffs between 35 and 40 are "arbitrary and unfounded."

"Potential kidney transplant recipients should not be excluded from UNOS transplantation solely on the basis of obesity; however, transplant patients [with obesity] should have careful optimization prior to surgery to minimize perioperative morbidity and reduce the likelihood of additional graft injury."

However, Lentine argued for considering both transplant center and patient-level factors in decision-making.

"I believe that obesity is prognostically important and potentially modifiable, but that it is also difficult to prescribe a one-size-fits-all threshold for candidacy across transplant programs," she said. She explained that not all centers have the expertise to manage patients with obesity during and after transplant or may have lower tolerance for surgical risks or for the potential elevated costs.

She argued for considering the potential risks and benefits of transplant for patients with obesity and engaging patients in shared decision-making.

"At a minimum, we advocate for lifestyle alterations such as healthy diet and appropriate exercise," she said. However, she noted transplant programs may have limited interactions with waiting list patients; so primary nephrologists may need to take a larger role. However, she noted there are few data to guide such interventions, and patients and physicians may have limited resources to pursue them.

[P]ursuing and maintaining healthy body composition based on guidelines for nutrition in renal failure are important priorities for kidney transplant candidates and recipients.

Pediatric perils

The data on the impact of obesity on pediatric outcomes have also been mixed. So, Heather Wasik, MD, a pediatric transplant fellow at Johns Hopkins University in Baltimore, and her colleagues conducted a retrospective cohort study using data from the Scientific Registry of Transplant Recipients, a US database of all donors, waitlist candidates, and recipients. They looked at recipients between 2 and 17 years of age to see if BMI categories were associated with outcomes.

They found that pediatric kidney transplant recipients classified as obese had the highest incidence of all cause graft failure at 37% at 10 years as compared with individuals who were normal or overweight at 34%, and those who were underweight at 32%.

"Based on these results, further study is warranted to evaluate whether weight-loss before or after kidney transplantation can result in improved graft survival in pediatric kidney transplant recipients," Wasik noted.

Lentine cautioned that "observational registry studies have not identified beneficial outcomes among ESRD patients who lost weight before transplantation; however, it is critical to recognize that association studies cannot distinguish intentional from unintentional weight loss as a result of illness and comorbidity, and offer little guidance on potential benefits of purposeful weight reduction."

"Prospective evaluations of the impact of intentional risk modification efforts are urgently needed, including dietary changes, monitored exercise programs, and bariatric surgery in obese patients," Lentine said.

Weight loss worry

Growing evidence that substantial weight loss is associated with a higher risk of mortality in patients with CKD and ESRD led Meera Harhay, MD, associate professor of medicine at Drexel University and her colleagues to find out whether weight loss may also be risky during the pretransplant period.

Harhay said there are many reasons patients may lose weight prior to transplant. Some may be intentionally losing weight to get below a hospital's BMI cutoff for transplant at the request of their physicians. Others may lose weight because of fluid removal during dialysis or because they have progressive sarcopenia and frailty.

"Each of these etiologies have links to potentially adverse outcomes," Harhay said. "Things like excess cardiovascular risk in our volume overloaded patients, excess inflammation in the frailty phenotype, and even malnutrition for patients who take on aggressive weight loss strategies in the setting of end state kidney disease."

To better understand how such circumstances may affect transplant outcomes, Harhay and her colleagues used United Network of Organ Sharing's national registry of adult deceased donor kidney transplants between 2005 and 2014. They found a steep increase in the risk of death among recipients who lost 10% or more of their body weight prior to transplant. When they adjusted for potential confounders like waiting time and dialysis vintage, they found those who lost 10% or more of their weight pretransplant had a 14% greater risk of dying posttransplant.

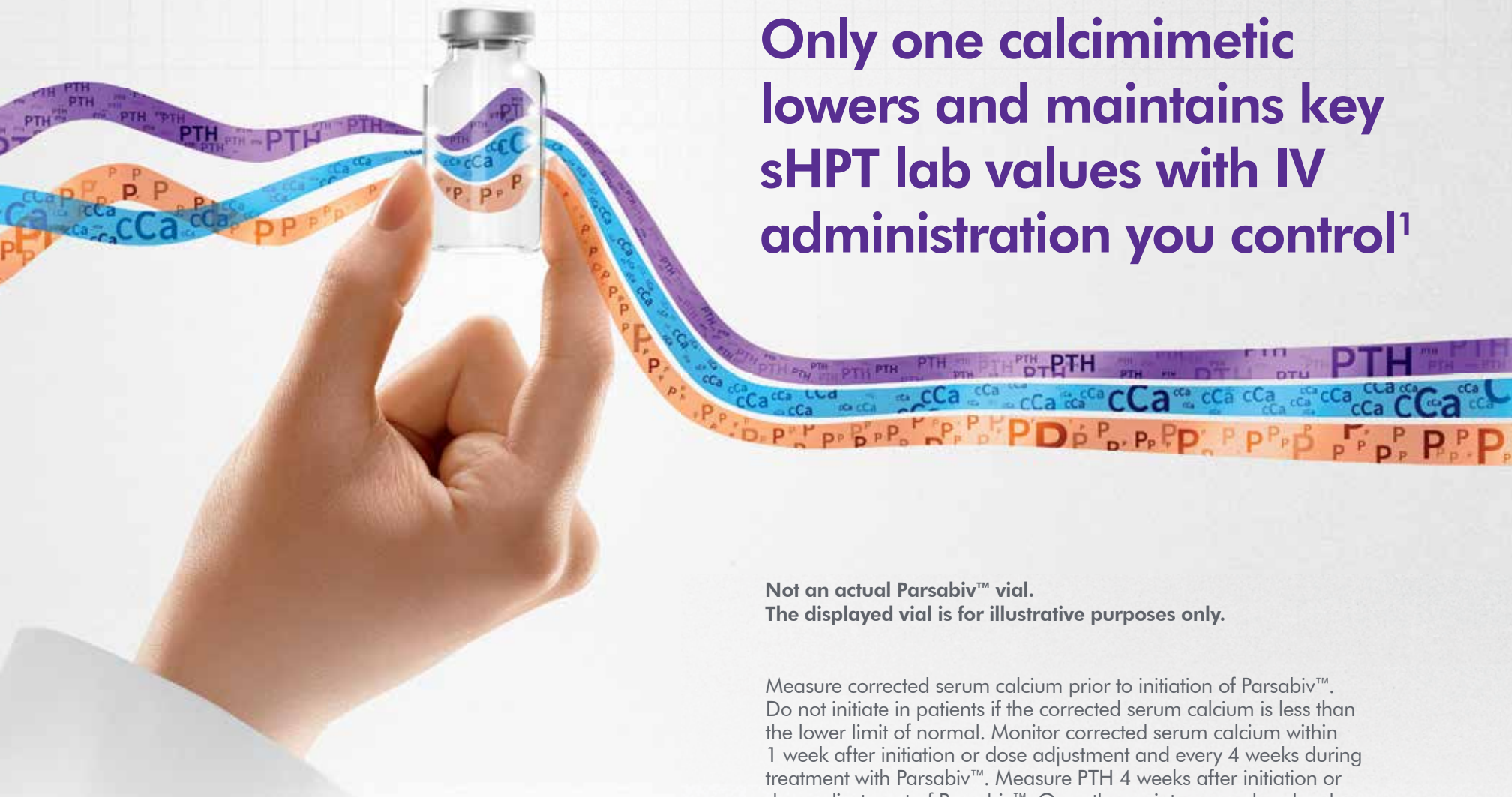
"Kidney transplant recipients with substantial pretransplant weight loss may benefit from closer surveillance posttransplant," Harhay said.

One limitation of the study is that it cannot disentangle intentional and unintentional weight loss, and obviously those etiologies are very different. But the increased mortality risk extended across BMI categories, Harhay noted.

"Obese and morbidly obese recipients who lost 10% of their body weight between listing and transplantation showed the same association of higher mortality risk, adjusted for all those factors, as did the underweight, normal weight that came onto the list and lost weight," she said.

Lentine emphasized the limitations of the available data to resolve these questions.

"I strongly advocate for ongoing research, including investigation of more accurate measures of body composition beyond BMI, and prospective studies, including prospective evaluations of intentional weight loss in patients who are obese," Lentine said. "For now, pending more evidence, I believe that pursuing and maintaining healthy body composition based on guidelines for nutrition in renal failure are important priorities for kidney transplant candidates and recipients."



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Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

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WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

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In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

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Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

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Higher Overdose Risk in Kidney Patients Prescribed Opioids, Benzodiazepines

Careful Prescribing, Alternative Treatments Recommended for Pain

By Bridget M. Kuehn

About 75% of patients on dialysis received a prescription for an opioid medication and nearly one-third of them also received prescriptions for benzodiazepines—prescribing patterns that were associated with a substantially increased risk of hospitalization for overdose, according to a study presented at Kidney Week.

More than half of patients on dialysis experience pain, according to a previous study (1), and more than 60% receive a prescription for an opioid medication each year—20% of those received a more than 90-day supply. A growing nationwide opioid overdose epidemic has drawn attention to the potential risks associated with this common class of drugs and led the US Centers for Disease Control and Prevention to establish guidelines for more judicious prescribing (2). But the safety of this class of drugs hasn't been well studied in patients on dialysis, said Rupam Ruchi, MD, assistant professor of medicine at the University of Florida.

"We know that pain affects so many of our patients, and it is associated with poor quality of life, increased morbidity, and mortality," Ruchi said.

Overdose

Now, Ruchi and her colleagues show that patients on dialysis are not immune to the potential overdose risks associated with opioids, particularly when they are given a concomitant prescription for benzodiazepines.

They looked at data from the US Renal Data System on hemodialysis patients enrolled in Medicare or Medicare's Part D drug program between 2006 and 2012. Patients with cancer were excluded. They also used data from the ESRD Medicare Prescription Drug Events dataset for narcotics and benzodiazepines, and they used ICD-9 codes to identify patients hospitalized for opioid overdose. Of the 643,859 patients included in the analysis 74.6% (480,460 patients) received an opioid prescription and 30% of them received benzodiazepines—a combination associated with an elevated overdose risk in the general population, according to the National Institute on Drug Abuse. Patients who received at least one opioid prescription were more likely than those who didn't receive opioids to have a history of smoking or substance use dependence.

Opioid prescriptions for patients in this population plateaued around 2011, when the CDC's opioid prescribing recommendations were published. But hospitalizations due to opioid overdose among these dialysis patients continued to rise, noted Ruchi.

Of those patients in the study with an opioid prescription, 2225 (0.46%) were hospitalized for an opioid overdose, and four of them died. The average length of stay was 4 days and the average length of ICU stay was 2. Patients on dialysis who received opioids were also more likely than those without an opioid prescription to overdose on other drugs, suggesting substance abuse may be more common in this group, noted Ruchi. Patients who were hospitalized for an opioid overdose were also more likely to have been prescribed a benzodiazepine than patients who were not hospitalized for an overdose, she said.

When they broke down opioid overdose risk by drug, they found that risk of hospitalization within 30 days was lowest with hydrocodone (OR 1.6), that fentanyl (OR 3.0) and hydromorphone (OR 2.4) had moderate risks, and that methydone had a very high risk (OR 5.9), according to the abstract. Oxycodone had a moderate risk (OR 3.1) while oxymorphone had a high risk (OR 4.5).

"All opioids increase the odds of hospitalization from opioid overdose in 30, 60, or 90 days of prescription," Ruchi said. "No opioid is safe to use in this population."

She noted that some of the opioids associated with higher odds of overdose among dialysis patients are considered "safer" drugs. This suggests a new classification system is needed.

"We propose using a risk-based classification instead of one based on pharmacokinetics," Ruchi said.

Magdalene Assimon, PharmD, PhD, postdoctoral fellow at the University of North Carolina Kidney Center in Chapel Hill, said the findings were cause for concern. She noted observational studies looking at other patient populations also have shown concurrent opioid and benzodiazepine use is associated with a higher risk of hospitalizations for opioid overdose than opioid prescriptions alone.

"Both opioids and benzodiazepines have sedating effects and increase the risk of respiratory depression," Assimon said. "Each of these side effects has the potential to impact morbidity and mortality and warrants additional investigation in the dialysis population."

[N]ephrologists [should] get to know their local pain center, which may be able to offer treatments like epidural steroid blocks or help with more complicated cases.

Safer pain care

In a separate talk as part of a session on primary care for patients with kidney disease, Kim Zuber, a physician assistant who specializes in pain care at Metropolitan Nephrology Associates, which serves patients in Virginia and Maryland, recommended a more holistic approach to treating pain. She noted that pain is often multifactorial in patients with kidney disease, so it is important to consider the source of the pain when determining how to treat it.

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Higher Overdose

Continued from page 9

"Up to half of our patients present with pain, and yet the problem is depression," Zuber said. "A third of them also have some type of anxiety."

She noted that CKD or end stage renal disease is a scary diagnosis. Patients may not recognize that they have these conditions, but clinicians may be able to tease out the symptoms if they ask in a diplomatic way.

"If we tone it into a particular way and we say you know, most of my dialysis patients, most of my CKD patients are depressed because of the situation, you'll find you'll get a higher number of patients who will admit it," she said.

The same is true with patients who may not be getting adequate sleep. Zuber said she often tells patients that she remembers how difficult things felt when she had an infant and was sleep deprived.

It's also important to set reasonable expectations for pain treatment.

"The pain centers will say to you the best we're ever going to do is maybe get down some of your pain by about 30% which means 70% of the pain we are not going to get rid of," Zuber said. "We do not expect to get rid of pain, we expect to make you functional."

Zuber recommended that nephrologists get to know their local pain center, which may be able to offer treatments like epidural steroid blocks or help with more complicated cases.

"I know the pain centers from one end of the US to the other and scarily they have never met the rest of you," she said. "They can help you and would love to meet you."

She noted that there are many pain treatment options to try besides opioids. For example, physical therapy can be a good option for patients with musculoskeletal pain. If patients can't get to a therapy center, Medicare may pay for home therapy. Cognitive behavioral therapy (CBT) is very effective, but there are a limited number of therapists available, Zuber noted. But social workers in the dialysis unit can get trained and certified in CBT. Lidocaine or lidocaine patches may ease conditions like post-therapeutic neuralgia. Capsaicin creams can also be used to dull nerve pain.

"Acetominophen works extremely well," she said.

In some states where it is legal, medical marijuana may be an option, Zuber noted. However, she noted there isn't much data on chronic pain treatment with the currently available medical marijuana products. While studies on alternative pain therapies like marijuana have been recently published, Assimon said more research is needed to fully understand the risks and benefits of such therapies in patients with kidney disease.

"If all else fails, fine opioids," said Zuber. "But they should not be your first go to. There's a whole list of things you can do prior to that."

Before a patient is given a prescription for opioids, they should be screened for current or past substance abuse, Zuber urged. She noted that there are validated brief screening tools available and that screening is reimbursable by Medicare.

She noted that urine tests for substance use might not be effective for patients with kidney disease. Many states now require physicians to check prescription drug databases to see if patients are already being prescribed opioids, however, she noted they might not provide information about prescriptions in neighboring states or the Veterans Health Administration. It is important to be mindful of patients who may be misusing prescriptions, Zuber said. She said she once received a call from law enforcement when a patient was caught selling his prescription for oxycodone and acetaminophen.

Zuber also urged that nephrologists choose opioids with better safety profiles, and avoid benzodiazepines.

"Don't give barbiturates and opioids together," she said. "Don't give barbiturates at all."

Assimon also recommended an individualized approach to pain care in patients with kidney disease that considers comorbid conditions, concurrent medications, and the type of pain a patient is experiencing.

"When selecting therapy for pain in patients with kidney disease, clinicians need to consider both the potential benefits and risks of medications under consideration," Assimon said. "Often this decision needs to be made on a patient-by-patient basis, taking into account each patient's type of pain, level of pain severity, and current risk factors for potential medication-related adverse effects."

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"Opioid and Benzodiazepine Use in Patients on Hemodialysis," Oral Abstract 095

Studies Examine Opioid Prescribing in CKD

Concerning national and regional patterns of prescribing opioids to patients with chronic kidney disease (CKD) were found in a pair of studies presented at Kidney Week.

A nationwide epidemic of opioid abuse and overdose has led to increased scrutiny of prescribing of this class of drugs. Patients with CKD are at increased risk of pain, and are more likely to be prescribed opioids than patients without kidney disease (7.5% vs. 5.4%), according to a study presented by Daniel Murphy, MD, Renal Diseases and Hypertension Fellow at the University of Minnesota.

Because opioids are cleared through the kidneys, their use among those with impaired kidney function may increase the odds of adverse effects, Murphy noted.

"We know that they're high-risk medications," he said. "We suspect that patients with chronic kidney disease may be at even higher risk potentially [than other patients]."

Despite these concerns, it appears that prescribing of opioids in kidney patients increased during 2011–2014 compared with 1999–2002, according to the study that analyzed 1999–2014 data from the National Health and Nutrition Examination Survey. The study also found increased use of opioids in patients with co-morbid conditions likely to cause pain, like cancer and arthritis, as well as in patients with conditions that may not directly cause pain, like diabetes, hypertension, and obesity. This might be because patients with multiple conditions interact with the health system more frequently, Murphy suggested.

"Patients who see lots of physicians have a higher opportunity to be prescribed opioids," he said.

But Phuong-Chi Pham, MD, chair of the division of nephrology at the University of California-Olive View, cautioned that diabetes can be associated with nerve pain. Pain might also contribute to the development of conditions like hypertension or obesity, or obesity could lead to back or knee pain, she said.

So, it is not entirely surprising that patients with CKD would be prescribed more opioids, Pham noted, because in addition to diabetic nerve pain, CKD is often associated with painful conditions like ulcers and vasculopathies.

Regional variations in opioid prescribing

Pham, however, was concerned by the results of a second study presented at Kidney Week that found substantial geographic variation in long-term opioid prescribing to older adults with CKD.

In the study, Yun Han, a graduate student in clinical pharmacy at the University of Michigan, and her colleagues looked at a linked data set of 5% of Medicare claims made between 2006 and 2009, the American Community Survey Data from 2005 to 2009, and the Health Resources and Services Administration Primary Care Service Area data from 2007.

They found that patients age 65 and older with a CKD diagnosis in the last year were more likely to be prescribed opioids for more than 90 days in the West and South. Additionally, counties with a larger population of older adults, higher poverty, or poor access to healthcare were likely to have more long-term opioid prescribing in this patient group.

"Our results highlight the importance of allocating resources for [the opioid] epidemic at the county level," Han said in a press statement. "The environmental factors identified in our study may be helpful for healthcare providers to target CKD patients at high risk of opioid abuse/dependence, and for designing local regulation and treatment for appropriate opioid use in CKD patients."

Pham said higher rates of long-term opioid prescribing in counties with more aging adults are to be expected. The concern is that counties with higher social deprivation and poorer healthcare access had unusually high rates of opioid prescribing. She noted one would expect lower rates of prescribing in areas with poorer access to care. This disconnect raises concern that there may not be enough subspecialists in these areas to treat the conditions causing pain or that patients may lack access to corrective procedures that could alleviate pain, she said. It also raises the possibility of recreational or other not medically indicated opioid use.

More data on the clinicians and institutions prescribing opioids in areas with poorer access to care may be useful, Pham said. Useful data might include how factors like academic vs. nonacademic institution, reimbursement type, patient volume, support staff, or physician characteristics including age, gender, or training are related to opioid prescribing.

"Most studies focus on patient and environmental factors, but we lack data correlating our healthcare systems to the use of opioids," she said. "Opioid overuse likely reflects a system as well as a patient/environmental problem."

Alternative medications, treating the source of pain recommended

Nephrologist Rob Foley, MD, associate professor of medicine at the University of Minnesota and principal investigator of the study Murphy presented, said prospective studies following CKD patients to determine when and why they start pain medications may be helpful, as would randomized trials of interventions to reduce the need for opioids through behavioral or other treatments.

In the meantime, it's important for nephrologists to be aware of concerns about opioid prescribing in this population, Foley said. He suggested that physicians consider the cause of the pain and try to treat the underlying problem. He also emphasized the importance of "stepping up" through less addictive medications first.

Murphy suggested using opioids for the shortest period necessary and revisiting pain concerns over time.

"Patients with chronic kidney disease do experience pain, but being thoughtful about how you are addressing pain in those patients and being wary of high-risk medications is important," Murphy said.

Pham suggested that nephrologists familiarize themselves with the high prevalence of pain in this population and special considerations with regard to treating it in patients with declining kidney function.

"Pain remains an important issue in the daily practice of medicine and more specifically in the general nephrology practice," she said. "Nephrologists need to achieve a relatively high level of competency in the routine management of pain."

Trials Examine Diabetes and Anemia Care in Later Stage Kidney Disease

By Bridget M. Kuehn

A pair of trials showed the diabetes medications linagliptin and bexagliflozin may be safe and effective at lowering blood sugar levels in diabetic patients with later stages of chronic kidney disease (CKD), according to late-breaking clinical trial results presented at Kidney Week 2018.

Other results presented at the late-breakers session tackled new strategies for treating anemia in dialysis patients and an intervention to reduce early dialysis. Another compared phosphate-binding medications.

Late CKD diabetes control

Although there are a growing number of medications available to manage blood glucose in patients with diabetes, finding one that is safe to use during the later stages of CKD has been a challenge. Diabetes is very prevalent in patients with CKD, said Vlado Perkovic, MBBS, PhD, executive director of the George Institute in Newton, Australia, noting there is a dearth of blood-sugar lowering drugs approved for use in the later stages of kidney disease. Those that can be used must be given in lower than optimal doses.

Perkovic presented results from the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) trial that examined the cardiovascular and renal safety of linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. In the trial, 6878 patients from 27 countries with type 2 diabetes—43% with estimated glomerular filtration rates (eGFRs) at 45 or below—were assigned to receive linagliptin or placebo in addition to usual care and followed for an average of 2.2 years.

"Linagliptin is entirely excreted by the liver and doesn't need dose adjustment; therefore it is particularly interesting as a potential therapy for improving glucose in people with existing kidney disease," Perkovic said during a press briefing about the trial. He noted that most other such therapies are filtered through the kidneys. In the trial, patients on linagliptin did see reduced albuminuria levels (hazard ratio 0.88 at 84 weeks) and albuminuria progression (hazard ratio 0.89) compared to those on placebo. The drug appeared to be safe from a cardiovascular perspective, Perkovic said, with no differences in cardiovascular outcomes between the drug and placebo.

"It didn't improve clinical renal outcomes though it did modestly reduce albuminuria, but it did improve glycemic control including in people with kidney disease," he said. "Therefore, it offers an important safe option for lowering blood glucose in people with reduced eGFR where there are few other options currently available."

However, Ian De Boer, MD, MS, director of the Kidney Research Institute at the University of Washington in Seattle who was not involved in the study, said the results provided a mixed message.

"There is, of course, great excitement in the new classes of glucose-lowering drugs and how they might improve renal and cardiovascular outcomes for people with type 2 diabetes," he said. "It was disappointing linagliptin had no significant effects on cardiovascular events or change in eGFR. It did show a reduction in albumin, which is hopeful, and perhaps over time could translate into kidney benefits. But the signal for kidney benefits in that trial was not as strong as we see for sodium-glucose co-transporter-2 (SGLT-2) inhibitors."

While SGLT-2 inhibitors have shown some benefits in terms of cardiovascular and renal outcomes in patients with diabetes, none have been approved for stage 3a and 3b CKD. There has been some question about their utility in later stages of kidney disease. Andrew Allegretti, MD, MSc, director of intensive care unit nephrology at Massachusetts General Hospital, explained that SGLT-2 inhibitors act on the kidneys to help remove glucose through the urine and are excreted by the kidneys, so declining kidney function might reduce their effects. Previous studies have shown that as kidney function declines, SGLT-2 inhibitors' hemoglobin A1c–reducing effects decline also, Allegretti noted.

But results Allegretti presented at Kidney Week show that the SGLT-2 inhibitor bexagliflozin appears both safe and effective in patients with diabetes and stage 3a/3b CKD. In the phase 3 trial, 312 patients with diabetes and stage 3a or 3b CKD from 54 sites were randomized to receive bexagliflozin or placebo for 24 weeks. The study found that bexagliflozin reduced hemoglobin A1c by 0.31% in patients with CKD stage 3a and 0.43% in patients with CKD stage 3b compared with placebo. It also lowered body weight by 1.61 kg, systolic blood pressure by 3.8 mm Hg, fasting plasma glucose by 0.76 mmol/L, and albuminuria by 20% on average. Adverse events were comparable between the drug and placebo groups.

Allegretti cautioned that the study wasn't designed to assess long-term effects, but he said it suggests that bexagliflozin may be an option for patients with later stages of CKD. He and his colleagues are currently trying to understand why bexagliflozin may work in this population when other SGLT-2 inhibitors have not.

"If we can use these drugs in later stage CKD patients, the hope is that we can have an easy to take agent that isn't an injection and doesn't have the weight increase insulin does and provides glucose-lowering and long-term end organ benefit," he said. "That's the hope for this class of drugs."

The findings suggest that at least some SGLT-2 inhibitors like bexagliflozin may work in patients with stage 3a and 3b CKD, De Boer said.

"I think this is going to promote more use of SGLT-2 in that population," he said.

He applauded the investigators of the CARMELINA trial for following patients longer term. He said more long-term studies of the use of newer diabetes medications in patients with kidney disease are needed as well as studies that look at clinical outcomes like cardiovascular disease or valid surrogates of clinical outcomes. De Boer said he'd also like to see more head-to-head trials of diabetes medications or drug combinations in patients with kidney disease.

"That's what really mimics the choices that practitioners and patients deal with in the real world," he said.

Treating anemia during dialysis

Nephrologists have shied away from using higher doses of erythropoiesis stimulating agents (ESA) to treat dialysis patients with anemia because of potential toxicities and increased risks of cardiovascular disease death, noted David Wheeler, MD, professor of kidney medicine at University College London. So, nephrologists have looked for alternative anemia treatment strategies.

"One trick nephrologists have learned is to give iron with the ESA so that you can reduce the dose of the ESA and the iron augments the erythropoietic effects of the ESA agent," Wheeler explained. "But we don't know how much iron to use and there are suggestions that if we give a lot of iron that we may be inducing toxicities or [increasing the risk of infections]."

At Kidney Week, Wheeler presented results from the Proactive Intravenous Iron Therapy in Hemodialysis Patients (PIVOTAL) trial that compared the effects of giving low dose or high dose intravenous iron to dialysis patients along with ESA. In the trial, 2141 patients in their first year of dialysis were randomized to receive either a proactive regimen of 400 mg of iron sucrose monthly unless ferritin levels rose above 700 g/L or TSAT scores were at or above 40%, or a reactive or low dose of intravenous iron only administered if ferritin fell below 200 g/L or TSAT fell below 20%. Physicians managed ESA levels as needed to maintain a hemoglobin between 10 and 12 g/L. Patients were followed on average for about 2 years.

The trial found that high dose iron reduces the average monthly dose of ESA by 20% without increasing cardiovascular events, infections, or mortality. Overall, the trial found that high dose iron was noninferior to low dose iron; however, high dose iron didn't reach the threshold for superiority to low dose iron.

"It is important that the intravenous iron in the proactive high dose regimen didn't increase the risk of infection or hospitalization and that was certainly a surprise to me," Wheeler said. "Whether this regime is safer in terms of preventing long-term cardiovascular outcomes and mortality we weren't able to prove; that requires a longer and larger study."

The results will likely promote more proactive use of iron in practice, De Boer said.

"We can be more liberal and more proactive in providing IV iron," he said. "That may improve outcomes, and may reduce costs."

However, De Boer cautioned that the results only apply to patients in their first year of dialysis and more study is needed to determine if the results extend to the wider population of dialysis patients.

Other high impact trials presented at Kidney Week 2018 showed that:

- Monthly dosing of a continuous erythropoietin receptor activator (CERA) was noninferior to more frequent doses of ESA to treat anemia in patients on dialysis in terms of all cause mortality and cardiovascular events. (Oral Abstract 145)
- An intervention to reduce early initiation of dialysis in Canada with academic detailing, audit and feedback, and visual aids for patients didn't work. (Oral Abstract 149)
- The non–calcium phosphate binder lanthanum carbonate didn't reduce cardiovascular events compared with calcium carbonate among patients on long-term hemodialysis with a high risk of vascular calcification (Oral Abstract 146)

"Effect of Linagliptin on Kidney and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Kidney Disease: CARMELINA®" Oral Abstract 142

"Safety and Effectiveness of Bexagliflozin in Type 2 Diabetes Mellitus and Stage 3a/3b CKD: A Phase 3 Randomized Clinical Trial" Oral Abstract 144

"High-Dose Versus Low-Dose Intravenous Iron Therapy in Hemodialysis: The PIVOTAL Trial" Oral Abstract 143

Precision Health Data May Help Curb Declining US Health Outcomes

By Brian Gonzalez

In the "new future" of medicine, data from patients, such as genetics, integrative physiology, digital phenotyping, and the environment, will be collected and tracked, then made readily available to clinicians, according to Robert M. Califf, professor of cardiology at Duke University School of Medicine and founding director of the Duke Clinical Research Institute. By the time a patient enters an exam room, the clinician will already have a "total background" on the patient that can inform treatment with a data trove that goes beyond the patient's self-description.

Dr. Califf, who describes himself as a data science politician, gave a state-of-the-art lecture on "Improving Health Outcomes in the Era of Data Ubiquity" at Kidney Week 2018. Dr. Califf was the Commissioner of Food and Drugs (FDA) in 2016–2017 and Deputy Commissioner for Medical Products and Tobacco from February 2015 until his appointment as Commissioner in February 2016. Dr. Califf is also employed by Verily Life Sciences, a division of Alphabet (the parent company of Google).

Dr. Califf laid out the current tailspin in US health outcomes:

- Life expectancy has declined for the third straight year.
- Geography and income continue to determine health outcomes and life expectancy.
- Premature deaths have increased 3% since 2015.
- Drug deaths have increased 7% in the past year.
- Cardiovascular deaths have increased 2% since 2015.

Additionally, midlife mortality from "deaths of despair," including drugs, alcohol, and suicide decreased or increased only slightly from 1989 to 2014 for white non-Hispanics across several developed countries including Germany, France, Sweden, Canada, the United Kingdom, and Australia. In contrast, midlife mortality from these causes for white non-Hispanics in the United States increased from approximately 35 to 80 per 100,000 deaths during this time period.

As life expectancy continues to decline in the United States, healthcare expenditures are near double those of similar high-income nations. Dr. Califf noted that these developed countries differ from the US in that most consider healthcare an actual right, a topic of debate in the US, and that most have a primary care system that functions well.

Tackling declining health outcomes and high expenditures

These declining health outcomes with high expenditures can be turned around in the US, Dr. Califf said, through what he calls "the fourth industrial revolution of the digital revolution": the fusion of technologies and a blurring of the lines of the physical, digital, and biological spheres.

With the combination of the human touch, clinical care, and quantitative capability built into our system, we will be in a much better place, he said.

"[T]his could be really, really good or really, really bad depending on how we adapt our human systems to deal with this technological revolution," he said, noting that "it will take a lot of human effort and culturally using the information to change what we do and measure the effect of that change."

Dr Califf advocated the need to integrate prediction science, social policies, incorporation of knowledge centrally, and economic considerations in order to find out how best to apply new therapies.

One way to do this would be to integrate all slices of the problem within a new system, such as Project Baseline, a partnership between Verily Life Systems, Duke University, Stanford University, and Google. Its ambitious aim is to measure the human condition and health outcomes and provide real-time information to data scientists, clinicians, policymakers, economists, students, and others.

The project consists of two phases for participants:

- An initial 2-day period of biometric testing to measure clinical labs, genomics, epigenomics, transcriptomics, immunophenotyping, microbiome, proteomics, metabolomics.
- Continuous measurement over time with gadgets like sleep sensors, wearables like smartwatches, and interactive cell phone technology that allows testers to ask participants about their health immediately instead of having them come to a clinic and recall how they felt in the past.

In addition to this fabric of constant observation that will measure the human condition, we are moving into an era where randomization will become the "routine business of understanding how treatments should work," Dr. Califf said. An example is PCORnet, which brings together patients, health systems, and payers to answer pragmatic questions. With this coordinated effort, patient groups could use data curated by health systems to answer their health questions and to further clinical trials. Currently, 25 large health systems in the US are part of this group, as well as HealthCore and Humana payers. Another example is the NIH Health Care Systems Research Collaboratory, which started in 2012 with the goal of developing methods and capacity for pragmatic or "real-world" clinical trials in the sense of generalizable findings, sustainable intervention, and efficient-cost trial conduct.

The hope is that a single individual's precision health data, when combined with data from households, neighborhoods, precincts, and states will then be used for analysis of actionable public health reforms to better address the tailspin of negative health outcomes in the US. ■

Studies Provide Comparative Data on Antidepressant Safety and Efficacy

By Bridget M. Kuehn

Sertraline may be more effective than cognitive behavioral therapy (CBT) for treating depression in patients on dialysis, according to a study at Kidney Week 2018. Another study found elevated heart risks with selective serotonin reuptake inhibitors (SSRIs) with greater QT-prolonging effects.

Almost one-quarter of patients on dialysis have depression, but many don't receive treatment, said Rajnish Mehrotra, MD, professor of medicine at the University of Washington in Seattle. One obstacle has been the dearth of data on depression treatment in patients on dialysis, who are typically excluded from clinical trials of antidepressants in the general population, noted Magdalene Assimon, PharmD, PhD, a postdoctoral fellow at the University of North Carolina Kidney Center in Chapel Hill. There have been few studies specifically exploring the comparative efficacy or safety of antidepressant therapies in patients on dialysis.

"We extrapolate both efficacy and safety evidence [from trials in other populations], which may or may not apply to patients on dialysis because of their unique situation with drug pharmacokinetics and their cardiovascular burden," Assimon said.

But the two studies presented at Kidney Week 2018 may help begin to close the knowledge gap.

CBT versus sertraline

During the High Impact Trials session, Mehrotra presented results of a multicenter randomized trial that began with depression screening for 2569 patients in 41 dialysis facilities across 3 metropolitan areas. The 636 patients with Beck Depression Inventory (BDI) scores greater than or equal to 15 were randomized to receive either a motivational interview about depression treatment or a brief encounter with a research staff member who alerted patients to their depression and asked if they would like to participate in a treatment study. The study found no significant difference in treatment initiation between those two groups (66% vs. 64%, respectively).

"It is possible that we pre-selected individuals [who] were interested in getting treatment anyway, and that is why we were not able to show a difference between people randomized to engagement versus control," Mehrotra said.

The 120 patients who decided to initiate therapy were then randomized to CBT or the SSRI sertraline. Patients receiving CBT were given the option of having a therapy session during dialysis or a separate private session. Both groups saw a decline in depression symptoms, but sertraline resulted in a greater decrease in depression symptoms as measured by the Quick Inventory of Depressive Symptoms (QIDS-C)—1.84 compared with CBT. Patients on sertraline also had more improvement on measures of disability, energy/vitality, life satisfaction, and sleep.

"In patients undergoing hemodialysis with major depressive disorder, depressive symptoms improved both with individual CBT and sertraline, but improvement was greater with sertraline," Mehrotra said.

However, sertraline was associated with a higher frequency of adverse events, he noted. Patients who received sertraline were more likely to be hospitalized and had threefold more mild and moderate adverse events than those receiving CBT. Mehrotra said he hopes the results help guide clini-

cians and patients on dialysis to choose the depression therapies that are the best fit for themselves.

"This comparative-effectiveness, randomized controlled trial could allow for informed decision-making by patients and physicians based on preference, cost, and availability," he said.

Assimon agreed that patient preferences are key in depression treatment. She noted that some patients may find it more convenient to take medication than undergo CBT.

"[The trial] is a step in the right direction, because it shows, again, that the drug is efficacious," said Assimon. However, she cautioned the study is likely not large enough to assess safety.

SSRI heart risks

Use of SSRIs in patients on dialysis who have depression will likely increase because of a new quality metric in Medicare's ESRD Quality Incentive Program that promotes depression screening and treatment, noted Assimon. But some drugs in the class have been associated with prolonged QT intervals in electrocardiograms of patients taking the medications, according to a drug safety communication from the US Food and Drug Administration (FDA). Prolonged QT intervals can lead to potentially deadly heart rhythm abnormalities, according to the FDA. Such adverse effects may be particularly concerning for patients on dialysis who are at increased risk of heart problems.

"The general consensus is that end stage renal disease creates a proarrhythmic environment," Assimon said.

To assess the heart risks of SSRIs, Assimon and her colleagues looked at 2007–2014 data from the United States Renal Data System on patients on dialysis enrolled in Medicare. They compared the risk of sudden cardiac arrest in the first year of taking citalopram and escitalopram, which have greater QT-prolonging effects, with the risk while taking fluoxetine, fluvoxamine, paroxetine, and sertraline, which have more modest effects on QT intervals. The study included 65,654 patients. Taking citalopram or escitalopram was associated with an increased 1-year risk of sudden cardiac death (adjusted hazard ratio 1.14; 95% CI: 1.05–1.25) compared to the SSRIs with lower QT-prolonging potential. Women, patients age 75 or older, and those with structural heart disease or taking additional QT-prolonging medications were particularly at risk.

"Our results suggest that SSRI therapy selection should be individualized, and clinicians should consider the differential QT-prolonging properties," Assimon said. For example, they should consider factors like age, gender, existing heart conditions, and concurrent medications when prescribing SSRIs. They may want to consider monitoring patients with ECGs.

Mehrotra also urged caution about potential QT-prolonging drugs, including SSRIs.

"It is important to be careful when using drugs that prolong QTc (whether SSRIs or others) in patients with end-stage renal disease," he said. "A significant proportion of patients undergoing dialysis have baseline QTc, and a longer QTc does increase risk for sudden cardiac death, the most common cause of death in patients undergoing dialysis."

He noted that he and his colleagues considered cardiac risk during the design phase of the trail. They chose sertraline because it has been used in large clinical trials of patients with congestive heart failure and coronary artery disease and was not associated with a higher risk of cardiac events.

"This reassured us when selecting the drug," he said.

"Comparative Efficacy of Therapies for Depression for Patients Undergoing Hemodialysis " Oral abstract 148

"The Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors (SSRIs) in the Hemodialysis (HD) Population" Oral Abstract 093

AKI Increases Long-Term Dementia Risk

By Bridget M. Kuehn

Patients who've recovered from acute kidney injury (AKI) have a 3-fold higher risk of developing dementia than hospitalized patients who avoid AKI, according to a study presented at Kidney Week 2018.

Patients who experience AKI may face long-term health complications even if they completely recover. Previous studies have shown that experiencing AKI increases the risk of developing chronic kidney disease (CKD) and cardiovascular disease. But the long-term consequences of AKI for brain health weren't clear.

"We used to think that almost all cases of AKI would have complete recovery, but now realize that many people have later development of CKD," said Hamid Rabb, MD, medical director of the Johns Hopkins Kidney Transplant Program in Baltimore. "Clinicians should be aware that AKI could have important kidney as well as non-kidney distant organ long-term effects, and therefore follow patients closely even after seeming resolution of AKI."

To assess the potential long-term effects on the brain, Jessica Kendrick, MD, associate professor at the University of Colorado School of Medicine, and her colleagues looked at 2082 patients without a history of dementia treated in an integrated health system in Utah between 1999 and 2009. During the study, which followed patients for a median of 5.8 years, 97 patients developed dementia. Those who had AKI were more likely to develop dementia than those who didn't (7.0% vs 2.3%). The hazard ratio was 3.4 (95% CI 2.14–5.40). The magnitude of the dementia risk was comparable to the risks of other long-term complications, noted Kendrick.

The study was "provocative" and needs to be confirmed by others, Rabb said. He noted it is not surprising that AKI might lead to an increased risk of dementia.

"AKI is well known to cause clinical changes in brain acutely, and some of these could lead to chronic changes," Rabb said.

Exactly how AKI might contribute to an increased risk of dementia is not clear. Kendrick noted it may be related to endothelial dysfunction after AKI. Now, she and her colleagues are looking at whether AKI may change cerebrovascular dynamics.

Rabb noted that patients with AKI may have other risk factors for dementia, such as diabetes, vascular disease, older age, or hypertension. Additionally, AKI is known to cause dysfunction in distant organs. Rabb suggested it might affect the blood-brain barrier, microglial activation, or protein leakage in the brain, which might contribute to dementia as well. He said it would be interesting to look at the renal function in patients who developed dementia compared with those who didn't, because it is possible they did not completely recover kidney function after AKI.

Kendrick noted it is also not clear how AKI contributes to other long-term complications like CKD or cardiovascular disease.

"It's an area that really needs to be investigated," she said.

Kendrick said it is important to research whether changes in the way hospitals care for patients with AKI could help prevent long-term complications, for example, whether more monitoring of kidney function after AKI would help identify patients' persistently elevated proteinuria.

"Even when people do well and recover, it's still associated with significant adverse outcomes," she said. "It would be nice to have something to offer them to hopefully prevent these complications from developing."

"Acute Kidney Injury is Associated with an Increased Risk of Dementia" (Abstract 3024328).

Polycystic kidney disease (PKD) is characterized by the progressive enlargement of numerous fluid filled cysts in the kidney. The 2 main types of PKD are ARPKD,* and the most commonly seen ADPKD.†[1,2]

In your patients with ADPKD

COULD KIDNEY DAMAGE BE GOING UNNOTICED?

eGFR‡ levels can remain steady over many years, but enlarging cysts continue to increase kidney volume, damaging renal tissue.[2,3]

Learn about the early signs of disease progression at UncoverPKD.com and screen your patients if you suspect they may be at risk.

*Autosomal recessive polycystic kidney disease.
†Autosomal dominant polycystic kidney disease.
‡Estimated glomerular filtration rate.

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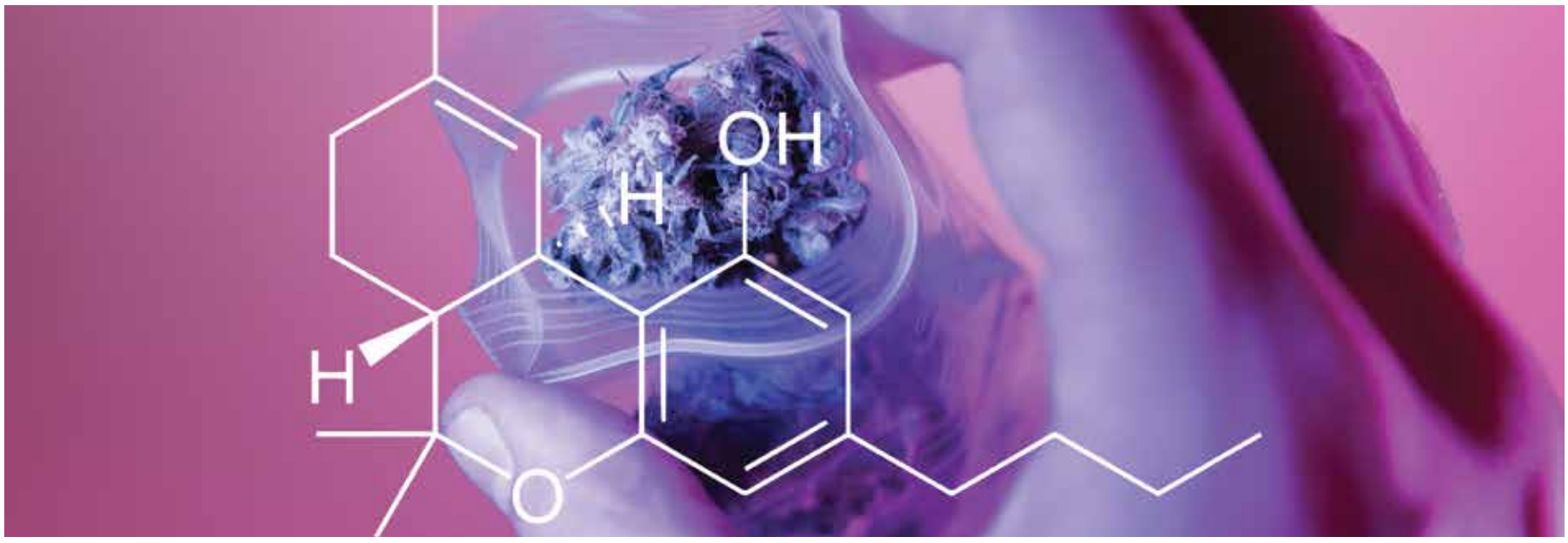

Cannabinoids: An Alternative Therapy for Managing CKD Symptoms?

By Mukta Baweja

It was a busy Wednesday afternoon in clinic in East Harlem, where the no-show rate can be as high as 50%, but this day it seemed like the show rate was more like 120%.

My patient panel for the day was diverse: from standard CKD management to managing the pitfalls of immunosuppression. Finally, my last patient of an exhausting day came in. One of my continuity patients with CKD stage 5, she came to partake in our monthly dance around the topic of dialysis access planning, which always starts well and ends with a fall.

"I know what that thing [fistula] in the arm is. My son just started on dialysis and has that in his arm," she said. "Do you still really think I need that? I saw something on a website that can cure my kidneys. Can't I try that?"

"Unfortunately, no, and I wouldn't take anything over the Internet, especially something that promises that," I replied.

"I know I have seen things in other countries that work. And people are growing kidneys all the time, she said. Maybe because you're a young doctor you don't know about these treatments, but that's what I want. Isn't there anything else I can do to get my kidneys back?"

Our answer to this question is too often in the negative, that we cannot do anything more for them.

We are limited in our medical management of symptoms of CKD, the side effects of our medications, and even the effectiveness of our treatments that are medicinally based. We have also grown to accept these unfortunate limitations as our standards of care. But is this acceptable? Are there alternatives in the treatment of kidney diseases, particularly with regard to symptom management and avoidance of dialysis?

After several visits involving counseling about dialysis planning, my patient came to me with full confidence that she had the answer to curing kidney disease, and was a bit annoyed with me that I had not told her about it. She had read about this miraculous drug on the Internet and had never felt better after taking it. The drug? Hydrogen peroxide.

To say that ingesting bleach is not curative is a bit of an understatement, and the potential harms could not be overstated. How could she turn to such a corrosive agent in an effort to avoid the treatment I had been recommending? She wanted something else to help her symptoms and provide an alternative to what I was offering. I don't know that I could blame her—what I was offering was a lifestyle change that included dialysis 3 to 5 times per week with a commitment of several hours each session and no guarantees that the rest of her day would not be consumed with traveling and pure posttreatment exhaustion. She just wanted a different option.

Can we do better to help our patients feel better and consequently have better outcomes?

It is quite understandable that our patients look to alternatives to the treatments we recommend. Our treatments, particularly immunosuppressants, come with considerable side effects, as well as high costs, and perhaps may not be as effective as we would like. And many patients, like mine, would do anything to avoid dialysis—even, apparently, ingesting bleach.

It is quite understandable that our patients look to alternatives to the treatments we recommend. Our treatments, particularly immunosuppressants, come with considerable side effects, as well as high costs, and perhaps may not be as effective as we would like.

The comorbid conditions that often plague our patients are many and are associated with considerable pain that in turn can often lead to opioid dependence, which has its own inherent set of problems. Not to mention the common symptoms in patients with CKD: nausea, insomnia, anorexia, and malnutrition, to name a few (1). International studies of CKD and ESRD patients have shown that more than 50% use alternative medicines to treat their underlying illness, and 40% of transplant recipients do the same (2). Physicians often fail to inquire about these alternative therapies, and also are likely not to be familiar with them, particularly herbal agents, although quite a few have been identified as clearly harmful. Yet, in 2018, we still have not been able to effectively manage symptoms, with or without these unknown alternative drugs.

Is there room for alternative care in nephrology? Is there something our patients can safely turn to in order to treat the pain associated with some symptoms of CKD?

Referred to by some as the "penicillin of the 21st century," or even the "turmeric of 2018," cannabis has shown some promise as an alternative in helping patients cope with chronic illnesses (3). Despite this, marijuana remains elusive in its potential—but only because it is federally illegal, thereby limiting the ability to test it in randomized controlled trials. The effects of marijuana use on kidney function have not been clearly defined, although there is evidence that cannabinoids can be as effective as codeine for pain management (4), and THC analogues have also been shown to be effective for chemotherapy-induced nausea and vomiting. Pain and nausea are two commonly reported and undertreated symptoms of patients with CKD, who perhaps may achieve the same benefit of treatment with cannabinoids as do patients experiencing side effects of chemotherapy, although this has not yet been studied.

It is not clear how many CKD and ESRD patients are currently using cannabinoids either recreationally or therapeutically. Given the potential therapeutic benefits without clearly defined harmful effects, it would seem cannabinoids may be a candidate for patients seeking alternative options in the management of CKD.

Cannabis is clearly not without its controversies, and it remains to be seen and understood who among our patient demographic might benefit from its use for medicinal purposes.

Seniors remain the largest demographic of patients with CKD, and increasing life expectancy comes with increasing comorbidities. Seniors also happen to be the fastest growing demographic of cannabis users (5). In addition to their heavy burden of comorbid conditions and associated symptoms, they also have more challenges to the practical aspects of living a life on dialysis, including transportation to and from treatments and the profound toll dialysis can take on quality of life. Older patients on dialysis are hospitalized more frequently, are more prone to experiencing symptoms, and have a reduced life expectancy compared to their younger counterparts under the age of 65.

As nephrologists, we are becoming more aware of the burden and intensity of care that is provided for older patients and consequently of the option for a more palliative approach to care, which may offer an improved quality of life at the expense of longevity (6). Despite this option, older patients often have consistently higher intensity treatments at the end of life rather than potentially alternative treatment courses that could be more appropriate.

It just might be possible that we can optimize the op-

tions for our patients by incorporating alternative care, such as with cannabinoids. As cannabinoids become more actively incorporated into society as a key player in the wellness industry, perhaps a key demographic target will be older patients seeking alternative approaches in their medical decisions, particularly when it comes to significant lifestyle choices such as initiation of dialysis. Perhaps a palliative approach to CKD and ESRD management would be more palatable if it could, in fact, be made more palliative?

According to the United States Renal Data System, Medicare pays an annual $55 billion for the population of CKD patients aged 65 or older, and $65 billion on all patients with CKD (1). This is an enormous cost, without an enormous benefit to patients, who remain with the same burden of symptoms and treatment options that have been relatively stagnant for decades.

The economic benefit to alternative care in nephrology is an area that has yet to be explored, but recent data have shown that cannabis has led to a considerable influx of revenue for state governments, which can be on the order of billions (7). Developments in the advancement of legalization of cannabinoids and continued growth in the US market should consider the voice of our patients, who are likely to grow increasingly dependent on the product in their pursuit of an alternative approach to care. Likewise, we may need to advocate this option as an extension of our other therapeutic options. At the very least, this option may prove to be an effective, if not a cost-conducive alternative.

Our patients are getting older, have more comorbidities, and also have an overwhelming burden of symptoms. We know that too often, we have to tell them that they "can't get their kidneys back." We know that many of our patients are already engaging in forms of alternative care without telling us. We know that sometimes those forms of care may be harmful, and that there are other types of alternative care that we just do not know that much about. We also know that there are potential benefits in some more controversial therapies such as marijuana, and we know that the astronomical costs of care in nephrology could use some control.

Even if we are not sure about the ultimate role of alternative care to help ease our patients' symptoms, such care is already making headway in nephrology and may be here to stay. ■

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Policy Update

Evaluation and Management Codes Undergo Changes

In November 2018, Medicare released the final Physician Fee Schedule (PFS) rule containing revisions to evaluation and management (E&M) code documentation requirements. Earlier, in a press conference announcing proposed E&M changes in July, Centers for Medicare & Medicaid Services (CMS) Administrator Seema Verma said, "Evaluation and Management or E&M visits make up around 40% of all Medicare payments under the Physician Fee Schedule, and guidelines have not been updated since 1997—21 years ago," adding that nearly 750,000 clinicians use these codes. "The requirements often mean that doctors have to cut or paste chunks of information across medical records strictly for billing purposes."

In service of CMS' stated goal of reducing documentation burden in E&M coding, CMS proposed to collapse levels 2–5 of E&M coding into one reimbursement payment. This move had negative implications for nephrologists and other clinician groups practicing cognitive care with complex patients.

After receiving more than 15,000 comments on the proposed rule, CMS finalized the rule so that for CY 2019 and CY 2020, CMS will continue the current coding and payment structure for E&M office/outpatient visits with clinicians using either the 1995 or 1997 E&M documentation guidelines. Additionally, for CY 2019 and beyond, CMS is implementing the following policies:

- Elimination of the requirement to document the medical necessity of a home visit in lieu of an office visit;
- For established patient office/outpatient visits, when relevant information is already contained in the medical record, clinicians may choose to focus on reporting on what has changed since the last visit, or on pertinent items that have not changed, and need not re-record the defined list of required elements if there is evidence that the physician reviewed the previous information and updated it as needed;
- Additionally, CMS clarified that for E&M office/outpatient visits, for new and established patients, clinicians need not re-enter in the medical record information on the patient's chief complaint and history that has already been entered by staff or the patient. The physician may simply indicate in the medical record that she/he reviewed and verified this information; and
- Clinicians are no longer required to duplicate notations in medical records that may have previously been included in the medical records by residents or other members of the medical team for E&M visits furnished by teaching physicians.

Beginning in CY 2021, CMS will further modify the coding and reimbursement for E&M office/outpatient visits. CMS has finalized the following policies set to begin in CY 2021:

- CMS will pay a single rate for E&M office/outpatient visit levels 2–4 for established and new patients while maintaining the payment rate for E&M office/outpatient visit level 5;
- Permit physicians to choose to document E&M office/outpatient level 2–5 visits using medical decision-making (MDM) or time instead of applying the current 1995 or 1997 E&M documentation guidelines, or alternatively practitioners could continue using the current framework;
- Beginning in CY 2021, for E&M office/outpatient levels 2–5 visits, clinicians will have flexibility in how to document visit levels—specifically a choice to use the current framework, MDM, or time. For E&M office/outpatient level 2–4 visits, when using MDM or the current framework to document the visit, CMS will also apply a minimum supporting documentation standard associated with level 2 visits. For these cases, Medicare would require information to support a level 2 E&M office/outpatient visit code for history, exam, and/or medical decision-making;
- When time is used to document, clinicians will document the medical necessity of the visit and the required amount of time face-to-face with the patient;
- Implementation of add-on codes that describe the additional resources inherent in visits for primary care and particular kinds of non-procedural specialized medical care, though they would not be restricted by physician specialty. These codes would only be reportable with E&M office/outpatient level 2–4 visits, and their use generally would not impose new per-visit documentation requirements; and
- Adoption of a new "extended visit" add-on code for use only with E&M office/outpatient level 2–4 visits to account for the additional resources required when extra time is required.

After omitting nephrology from the list of specialties dealing with complex patients that could use an add-on code for complexity in the proposed rule, CMS wrote in the final rule that "We also agree with commenters that the code descriptor omitted several specialties that provide this type of visit, such as nephrology, psychiatry, pulmonology, infectious disease, and hospice and palliative care medicine…. As discussed previously, appropriate reporting of the specialty care resource add-on code should be apparent based on the nature of the clinical issues addressed at the E/M visit, and not limited by the practitioner's specialty."

The ASN Quality Committee will continue to analyze this rule further. ■

Fellows Corner

Interviewing Women Physicians: It's Time to Level the Playing Field

By Natasha N. Dave

Natasha N. Dave

Twenty years ago, a young newlywed senior nephrology fellow set out on a job interview. She sat down with the practice's senior partners, who asked her general interview questions, including, "Why are you interested in joining our practice?" and "Where do you see yourself in five years?"

The interview was going well, and she began to feel the practice was right for her. As the interview came to a close, one male partner asked, "When do you plan on having children, and how many do you plan to have?"

She said she was unsure about exactly when she would have children and asked why the interviewer was curious. He answered, "Well, we need 100% commitment from you for the first two years. After two years of employment, and if you make partner, you can think about having a couple of them."

Statements like these were not uncommon at the time. The woman said she understood and thanked them for their time. She later joined their group and worked tirelessly, taking a total of 12 days off during her first two years of practice. Once she made partner, she used all of her accrued vacation days and gave birth to her first child. Situations like this are unfortunate, but they continue to happen, even to this day. Even to me.

During my final year of fellowship, I looked forward to interview season more than anything. It was the light at the end of the tunnel that took over a decade to build.

It wasn't until I was being interviewed that I realized some practices didn't see me as a physician. They saw me as a woman. I was asked questions like these: "How old are you?" "Are you married?" "What does your husband do?" and "When do you plan on having children?"

Bewildered, I asked around and learned I was not alone. A friend and fellow applicant shared her experiences, stating that during her interview she was asked, "Your reference mentioned you have 3 children; how do you plan on balancing this job and all your kids?" Even outside my circle of friends, I found a whole arsenal of women in healthcare who have had similar experiences.

The #MeToo movement has inspired women who have experienced sexual harassment to come forward in Hollywood, and the #MeTooInMedicine movement has led women in healthcare to shed light on this matter as well. Multiple groups of women in healthcare have also come together online to discuss various workplace gender-related issues. Recently the hashtag #QuestionsIveBeenAskedAsA-Woman surfaced on Twitter, exposing sexist questions women have been asked during work hours, during meetings, and during interviews.

Although female physicians are no stranger to employment discrimination, both federal and state laws prohibit it. The Civil Rights Act of 1964 prohibits discrimination based on race, color, religion, sex, or national origin. Furthermore, the Civil Rights Act was amended to include the Pregnancy Discrimination Act in 1978, allowing women affected by pregnancy, childbirth, or related medical conditions to be treated the same as other employees for all employment-related purposes.

The Family and Medical Leave Act (FMLA), which passed in 1993, prohibits discrimination for specific family and medical reasons including birth of a child, care of a newborn, and care of a family member with a serious health condition. Despite this prohibition, employers continue to ask women about their marital status and child-rearing plans during interviews. Other examples of prohibited questions include those about birth control, childcare arrangements, and a spouse's job.

Employers should ask questions that assess an applicant's job qualifications. They should avoid asking any questions of their female applicants that they do not ask of their male counterparts. Female applicants should prepare themselves in anticipation that a prohibited question may be asked during an interview. According to www.FindLaw.com, here are steps you may take if as an applicant you are confronted with such a question:

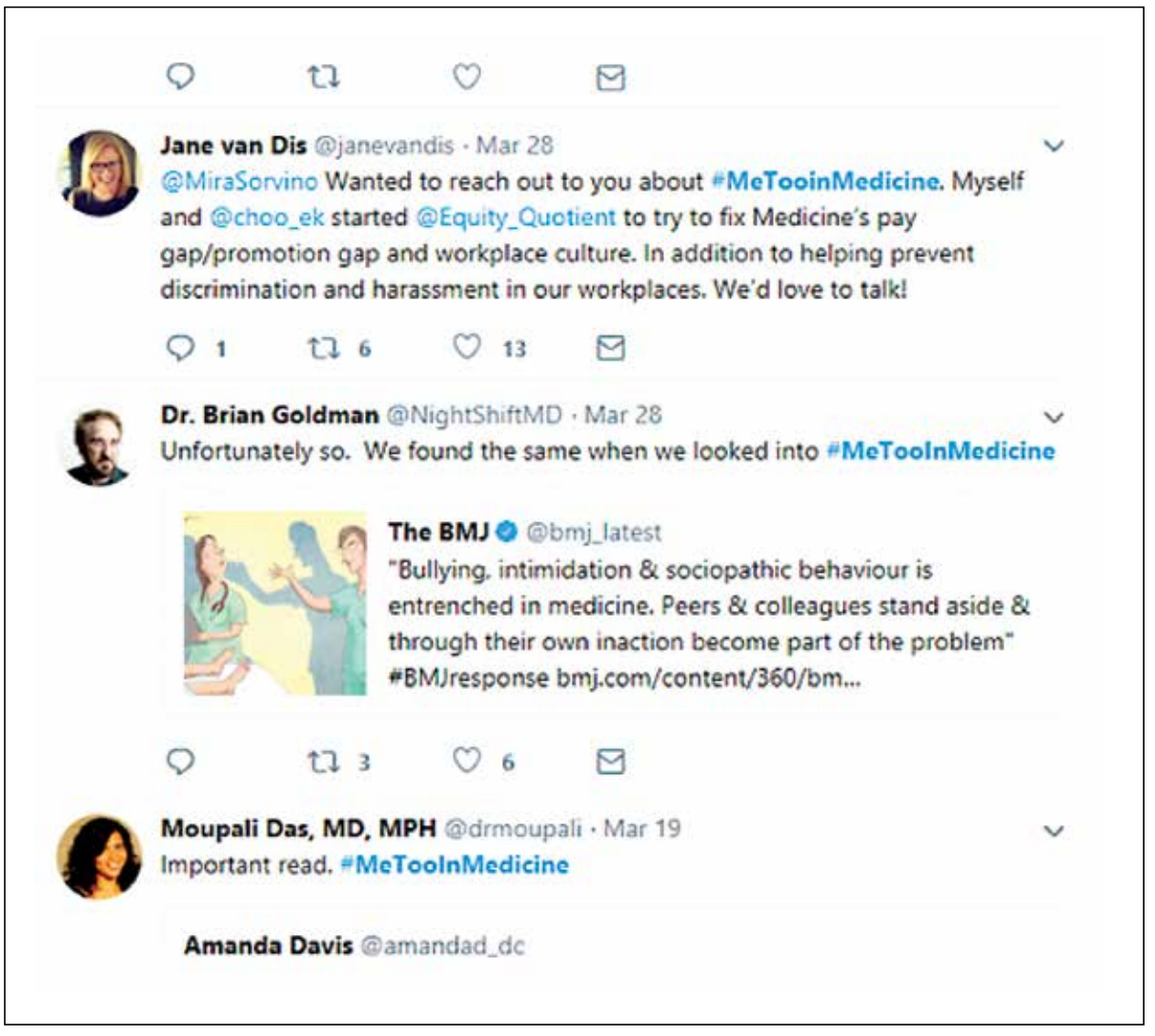
- Answer the question and move on.
- Ask the relevance of the question to the position.
- Question the intent of the question by asking about the employer's underlying concern.
- Explain that you are not comfortable answering that type of question.

Entering the workplace as a woman physician has its own unique set of struggles, but working toward the goal of equality is worth striving for. As my interview season came to an end, I found that my interview at a Veterans Affairs (VA) Hospital was surprisingly one of my best experiences. The VA asks all applicants standardized questions that have been deemed appropriate for the job they are seeking.

It is time for employers to reevaluate their interview methods and try to adopt a fair process for hiring new physicians. Such a process would respect each applicant. It would not place likability and capability at odds. And it would not engender concealment for fear of being passed over, while providing the employer with the necessary information to make an informed decision. ■

Natasha N. Dave, MD, is a fellow at Baylor College of Medicine.

Figure 1. The ongoing Twitter discussion of the #MeTooinMedicine



Innovation in Transplantation: Accountability, Collaboration, and the Value of the Patient Voice

By Kevin Fowler

On September 27 and 28, 2018, the Food and Drug Administration (FDA) convened and facilitated the workshop "Evidence Based Treatment Decisions: The Right Dose and Regimen—the Right Patient/ Individualized Treatment." The focus of the workshop was on the patient, specifically on utilizing biomarkers during the drug development process to determine the right treatment regimen to prevent long-term rejection of the patient's transplanted organ. I participated in the meeting on behalf of the Kidney Health Initiative (KHI) as Vice-Chair of the Patient Family Partnership Council (PFPC).

The workshop was the byproduct of two factors. The first was the creation of the Transplant Therapeutic Consortium (TTC) in March 2017. The TTC was launched to identify and develop mechanisms to accelerate drug discovery for transplant through the collaborative involvement of key stakeholders in the field, first focusing on kidney transplant. The TTC is part of the Critical Path Institute (CPI), founded in Tucson, Arizona, in 2005 as an independent nonprofit dedicated to bringing together experts from regulatory agencies, industry, and academia to collaborate and improve the medical product development process.

The second element contributing to the workshop was the FDA's commitment to help facilitate innovation in the transplant community. The FDA has conducted transplant workshops for the past four years:

- 2015: "Surrogate Endpoints for Clinical Trials in Kidney Transplantation"
- 2016: "Patient Focused Drug Development in Patients Who Have Received an Organ Transplant"
- 2017: "Antibody Mediated Rejection in Kidney Transplantation"

With the exception of the 2017 FDA Transplant Workshop, I have attended every meeting. Unlike the previous FDA meetings, the 2018 workshop left me with a clearer sense of the path to drug development, and to delivering unmet patient and medical needs. My vision was formed based upon the following three meeting observations:

Accountability of American Society of Transplantation/American Society of Transplant Surgeons

Ulf-Meier-Kriesche, MD, Chief Scientific Officer of Veloxis and a transplant nephrologist, acknowledged during his presentation that the current transplant clinical endpoint, one year acute rejection rates, has been diminished significantly in utility and value. He acknowledged that it is very difficult to exceed the one year acute rejection rates established by cyclosporine and tacrolimus. Acute rejection is a high bar for pharma companies to exceed thereby influencing their reluctance to invest in transplant therapeutics. Moreover, Dr. Ulf-Meier-Kriesche made clear that it is the responsibility of the transplant community to establish clinical endpoints relevant to today's clinical practice, and to pharma innovators.

Collaborative Approach

The TTS and, by extension, the CPI, developed a 2-day workshop notable in its collaborative agenda. Unlike previous meetings where the agenda was conducted by the familiar transplant professionals, at the TTC these familiar voices were complemented by professionals from oncology and CKD, and by transplant professionals from Europe. The infusion of different voices and disciplines brought a much needed breath of fresh air to the meeting, and a different way of approaching innovation. I would like to recognize the efforts of Kenneth Newell, MD, PhD, Professor of Surgery, Division of Transplantation, Department of Surgery, Emory University; Peter Nickerson, MD, Flynn Family Chair in Renal Transplantation at the University of Manitoba; and Rita Alloway, PharmD, Research of Nephrology, University of Cincinnati, who had the wisdom to look outside the transplant community for answers.

There was one new voice that stood out at the meeting: Alexandre Loupy, MD, a transplant nephrologist from Paris and a member of the Paris Transplant Group. The Paris Transplant Group is developing a personalized transplant medicine approach that integrates multiple sources of information including classical histology and biology, as well as novel information from molecular biology, immunology, and genetics and biomarkers. In essence, the Paris Transplant Group is providing leadership not only in precision medicine but in an integrated approach to transplant patient care and improvement in patient care guidelines. Like most of medicine, transplant medicine has been practiced reactively. This collaborative approach is a welcome shift in the future practice of transplant medicine.

At the FDA meeting, Dr. Loupy presented the final product proposed by the Paris Transplant Group, the "Ibox." Rather than estimating prognostic allograft survival based upon serum creatinine function and proteinuria, the Ibox expands the sources of information, thereby developing a comprehensive picture of the patient's transplanted organ. Based upon the varied sources of information, the Ibox has the ability to develop a prognostic score and accurately predict individual long-term graft survival. Dr. Loupy presented how the Ibox had potential applications in the development of clinical trial endpoints in transplantation. The prognostic ability of the Ibox has the potential to examine how investigative transplant medications may have an impact on long-term kidney transplant outcomes, thus serving as a cost-effective alternative to long-term kidney transplant trials. I considered Dr. Loupy's presentation the brightest light at the meeting.

Value of the patient voice

One tangible outcome of the 2016 FDA Transplant Workshop was "The Patient Voice Report: Patient-Focused Drug Development in Patients Who Have Received an Organ Transplant." The report serves as a source of information on the treatment burdens that the handful of FDA-approved transplant medications impose upon people living with a transplanted organ. This document was referenced several times by the presenters.

A conversation I had with Mark Stegall, MD, Professor, Transplant Surgery, Mayo Clinic, reinforced my belief that the transplant community has enhanced its understanding of people living with a transplant. Dr. Stegall understands the significance of cognitive impairment that occurs with kidney disease and that is further accentuated by the cognitive impact of one of the approved transplant medications. The limitation of current medications could provide a path to approval for new medications, Dr. Stegall noted.

While I left the meeting optimistic that there is a path to bring innovative medications to the transplant community, I would like the TTC to consider one thing. While people living with a transplant were represented at the meeting, a patient voice strategy was not apparent. The TTC can learn valuable lessons on developing a patient voice strategy from KHI and the PFPC. We are happy to share our lessons.

Kevin Fowler is the Vice-Chair of the KHI PFPC, and President and Founder of "The Voice of the Patient." He can be reached at kevinjohnfowler@gmail.com and you can follow him on Twitter @gratefull080504.

Review Questions Evidence on Statins for Non-CVD Outcomes

There is a "dearth of convincing evidence" that lipid-lowering treatment with statin drugs plays any major role in improving outcomes other than cardiovascular disease (CVD), concludes a review and meta-analysis in *Annals of Internal Medicine*.

The researchers report an "umbrella" review of 268 previous meta-analyses of data on non-CVD outcomes of statin treatment. Their review identified 144 papers reporting 297 meta-analyses of randomized controlled trials (RCTs) and 112 papers reporting 268 meta-analyses of observational studies. The analysis examined a total of 278 unique non-CVD outcomes. It included credibility assessments incorporating summary effect sizes, study heterogeneity, 95% prediction intervals, study size, and significance bias.

On analysis of RCT data, there was only one significant statin-related non-CVD outcome with a sufficient amount of evidence and no sign of bias: reduced all-cause mortality in patients with chronic kidney disease. Analysis of observational data found no "convincing" associations and two "suggestive" associations: decreased cancer mortality in patients with cancer and decreased exacerbation rate in patients with chronic obstructive pulmonary disease. The observational data also showed "weak" associations for 42 additional non-CVD outcomes.

Analysis of adverse events in the RCT data found no effects of statins on risks for myopathy, myalgia, or rhabdomyolysis. For the observational studies, there was "suggestive" evidence for increased risks of diabetes and myopathy.

Statins have well-demonstrated benefits in reducing the risk of heart disease and stroke. Although many studies have suggested that statins can improve various non-CVD outcomes, the evidence supporting these benefits is less clear.

Only a few of the reported effects of statins on non-CVD outcomes show convincing evidence of a credible association, according to the umbrella review of existing meta-analyses. Even the reduction in all-cause mortality in chronic kidney disease might be attributable to CVD events, the authors suggest. They conclude that their findings "do not support any change in the existing clinical recommendations regarding statin use for non-CVD conditions" [He Y, et al. Statins and multiple noncardiovascular outcomes: umbrella review of meta-analyses of observational studies and randomized controlled trials. *Ann Intern Med* 2018; 169:543–553].

No Increase in CKD Risk with Allopurinol for Gout

For patients with gout, starting urate-lowering therapy with allopurinol does not appear to lead to an increased risk of developing stage 3 or higher chronic kidney disease (CKD), reports a study in *JAMA Internal Medicine*.

Using a UK general practice database, the researchers identified two propensity-score matched groups of patients with newly diagnosed gout. One group of 4760 patients initiated urate-lowering treatment with allopurinol. The comparison group included the same number of patients who did not receive allopurinol. About 83% of patients in both groups were men. Mean age was 57 years and mean body mass index was 30. All patients had initially normal or near-normal kidney function.

The main outcome of interest was the development of stage 3 or higher CKD. Mean follow-up was 5 years in patients who initiated allopurinol and 4 years in the comparison group.

Patients starting allopurinol at a dose of at least 300 mg/d were less likely to develop stage 3 or higher CKD: adjusted hazard ratio 0.87. There was little or no difference in the association after additional adjustment for the covariates included in the propensity score. At initial doses of less than 300 mg/d, allopurinol therapy showed no association with decline in renal function.

Only one-third of patients with gout receive urate-lowering therapy; the problem of undertreatment is compounded by frequent comorbidity with CKD. Physicians are cautious about using allopurinol in patients with gout, especially those with declining renal function. There is a lack of data on the renal effects of allopurinol in gout patients with normal renal function.

This large study analysis of primary care data finds a reduced risk of stage 3 CKD among newly diagnosed gout patients starting on allopurinol, 300 mg/d or higher. The researchers discuss their findings in the context of the ongoing suboptimal treatment of gout. They conclude: "Because allopurinol does not appear to be associated with renal function decline, clinicians should consider evaluating other potential causes when patients with gout experience renal function decline" [Vargas-Santos AB, et al. Association of chronic kidney disease with allopurinol use in gout treatment. *JAMA Intern Med* 2018; 178:1526–1533].

ACEI/ARB Treatment May Lower Mortality after AKI

In patients with acute kidney injury (AKI), treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) is associated with a lower risk of death but an increased risk of kidney-related hospitalization, reports a study in *JAMA Internal Medicine*.

The study included 46,523 adults who had an episode of AKI in the hospital between 2008 and 2015, identified through the Alberta Kidney Disease Network database. All included patients survived to hospital discharge without end stage renal disease (ESRD). Mean age was 68.6 years; 52.8% of patients were men.

Forty-eight percent of patients were prescribed an ACEI or ARB within 6 months after hospital discharge. Mortality and secondary outcomes were compared for propensity score-matched groups of patients who did and did not receive ACEI/ARB treatment.

With at least 2 years' follow-up, patients receiving an ACEI or ARB after AKI were at lower risk of death. Hazard ratio (HR) for mortality was 0.85, with adjustment for comorbid conditions, preadmission ACEI/ARB use, demographic factors, initial renal function, other factors related to hospitalization, and previous healthcare use. Both new and continued ACEI/ARB use were associated with lower mortality.

However, the ACEI/ARB group also had an increase in renal-related hospitalizations: adjusted HR 1.28. Major causes of hospitalization included acute renal failure, congestive heart failure, and hyperkalemia. Treatment with an ACEI/ARB after AKI was unrelated to the risk of progression to ESRD or doubling of serum creatinine.

Strategies are needed to reduce long-term mortality after AKI. These population-based data suggest that patients receiving ACEI/ARB therapy are at lower risk of death but higher risk of hospitalization for kidney-related causes. The researchers conclude, "These results suggest a potential benefit of ACEI or ARB use after AKI, but cautious monitoring for renal-specific complications may be warranted" [Brar S, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. *JAMA Intern Med* 2018; doi:10.1001/jamainternmed.2018.4749].

Should Catheters Be Replaced in Patients with UTI?

Routine catheter replacement does not improve outcomes for hospitalized patients with catheter-associated urinary tract infection (UTI), according to a report in *Journal of the American Geriatric Society*.

The prospective, observational cohort study included 315 patients who developed a symptomatic UTI after having an indwelling urinary catheter in place for longer than 1 week. The patients, mean age 79.2 years, were being treated in six internal medicine departments and the geriatric department of an Israeli university hospital. Most were residents of a nursing home or other long-term care facility; they had high comorbidity, with a median Charlson score of 3.

In 98 patients, the catheter was removed and replaced within 6 hours, based on department practice. In the remaining 217 patients, the catheter was left in place. The main outcome of interest was clinical failure, defined as death or clinical signs or symptoms of sepsis within 7 days. The two groups were matched using a propensity-score model for catheter replacement.

The 7-day clinical failure rate was 35.2% and 30-day mortality 30.8%. Neither outcome was significantly different for patients who did and did not undergo catheter replacement. The results were similar on subgroup analyses of patients with more than 30 days of catheterization and those with definite catheter-associated UTI. There were no adverse outcomes associated with catheter replacement. Patients with catheter replacement spent a median of 2 more days in the hospital.

There are no universally accepted guidelines for managing symptomatic UTI in patients with long-term urinary catheters. While catheter removal and replacement may be a reasonable strategy, there are potential harms of routine catheter removal.

This study questions the benefit of replacing long-term catheters in hospitalized patients at the onset of catheter-associated UTI. The researchers conclude, "Until a randomized controlled trial in the relevant population shows otherwise, we see no reason to support routine replacement of a long-term urinary tract catheter in individuals with a symptomatic UTI" [Babich T, et al. Replacement of urinary catheter for urinary tract infections: a prospective observational study. *J Am Geriatric Soc* 2018; 66:1779–1784].

Industry Spotlight

FDA round-up

Two companies have been given the thumbs-up by the U.S. Food and Drug Administration (FDA) for kidney-related therapies. Hansa Medical (Lund, Sweden) has been granted FDA Fast Track Designation for its drug candidate imlifidase to help reduce kidney rejection in transplantation. Under this designation, the FDA process is designed to facilitate development and expedite the review of drugs that could treat serious conditions and fill an unmet medical need. Another company, MediBeacon Inc. (St. Louis, MO) has been granted a Breakthrough Designation for its transdermal measurement device for GFR, a designation given when a product may show improvement over available therapy.

Hansa Medical's compound imlifidase is an enzyme in late-stage clinical development as a treatment to enable kidney transplantation for sensitized patients who previously were unable to undergo transplantation because of certain donor-specific antibodies.

"This Fast Track Designation is validation of imlifidase's potential to address the significant unmet medical need for highly sensitized patients, a patient population for which transplantation is extremely difficult or impossible," said Søren Tulstrup, president and chief executive officer of Hansa.

Efficacy data from four phase 2 studies demonstrated that imlifidase rapidly and significantly reduced donor-specific antibodies by cleaving IgG, enabling transplantation.

The company notes that current desensitization methods are not feasible for most highly sensitized patients.

MediBeacon Inc., whose largest shareholder is Pansend Life Sciences of HC2 Holdings, announced that the FDA has granted Breakthrough Device designation to MediBeacon's Transdermal GFR Measurement System (TGFR). The device is intended to measure GFR in patients with impaired or normal renal function.

The FDA designated MediBeacon's TGFR a combination product that includes an optical skin sensor, monitor, and MB-102, a proprietary fluorescent tracer agent that glows in the presence of light. The TGFR is designed for continuous real-time measurement of GFR at the point of care, without blood or urine collection.

"We are delighted that the FDA has recognized that the Transdermal GFR Measurement System meets the requirements for this designation," said Steve Hanley, MediBeacon CEO. "We look forward to continued close collaboration with the FDA as we begin our pivotal multicenter clinical study in the United States and Europe."

DaVita division will pay $270 million settlement

HealthCare Partners Holdings LLC, part of DaVita Inc., must pay $270 million to settle an allegation involving Medicare Advantage insurance plans.

According to a news release from the U.S. Department of Justice, DaVita Medical Holdings agreed to pay the money to resolve its liability under the False Claims Act. The Justice Department reported that HealthCare Partners provided "inaccurate information that caused Medicare Advantage Plans to receive inflated Medicare payments."

Medicare beneficiaries have the option of enrolling in and obtaining health care from Medicare Advantage Plans that are owned and operated by private Medicare Advantage Organizations (MAOs). To provide the patient care, MAOs may contract directly with physicians and other healthcare providers, or they may contract with Medical Services Organizations, which in turn either employ or contract with healthcare providers.

DaVita operated a Medical Service Organization and contracted with MAOs in various states, including California, Nevada, and Florida, to provide care to the MAOs' enrolled Medicare beneficiaries. In connection with the medical services it provided to those beneficiaries, DaVita collected and submitted diagnoses to the MAOs. As payment for its services, DaVita received from the MAOs a share of the payments that the MAOs received from the Centers for Medicare & Medicaid Services for the beneficiaries under DaVita's care.

A whistleblower alleged that HealthCare Partners engaged in "one-way" chart reviews in which it scoured its patients' medical records for diagnoses its providers may not have recorded. It then submitted these "missed" diagnoses to MAOs, which in turn obtained increased Medicare payments. At the same time, HealthCare Partners ignored inaccurate diagnosis codes that should have been deleted and that would have decreased Medicare reimbursement or required the MAOs to repay money to Medicare.

DaVita says the settlement "reflects close cooperation with the government to address practices largely originating with HealthCare Partners," Kaiser Health News reported.

DaVita noted in a recent filing with the Securities and Exchange Commission that the settlement would be paid through escrow funds established in connection with DaVita's merger with HealthCare Partners in 2012.

Study of novel FSGS compound

A new study called FirstX is now enrolling participants and will examine a compound called CXA-10 in primary FSGS as a first-line drug for people who would normally have been treated with high-dose steroids. CXA-10 is in a class of oral compounds called nitrated fatty acids. It is a signaling agent with anti-inflammatory/immunomodulatory, antifibrotic, antioxidative, and other properties that are important in the pathobiology of FSGS, according to an abstract for the trial presented during ASN Kidney Week 2018.

Primary FSGS is often treated with steroids, but side effects of prolonged use may include obesity, hypertension, growth impairment, diabetes, and immune suppression.

A phase 2, multicenter, randomized, open-label study, FirstX will evaluate the efficacy and safety of CXA 10 in approximately 30 participants. The study is sponsored by clinical-stage biopharmaceutical firm Complexa Inc. in Berwyn, Pennsylvania. Eligible patients include adults with biopsy-proven primary FSGS who have not received treatment for FSGS with high-dose, long-term steroids (or other immunosuppressive therapy). Patients will be randomized into one of two possible groups and will receive CXA-10 treatment for 3 months. The primary efficacy endpoint is reduction in proteinuria. Other efficacy endpoints include markers of nephrotic syndrome, kidney function (estimated GFR), biomarkers relevant to the disease, and patient-reported outcomes.

Complexa is partnering with the Kidney Research Network, University of Michigan Data Coordinating Center, and NephCure Kidney International to conduct the trial.

High National Rates of Missed Hemodialysis Linked to Poor Outcomes

Countries with high rates of missed hemodialysis (HD) treatments have elevated rates of death and other adverse outcomes, reports a study in *American Journal of Kidney Diseases*.

The researchers analyzed data on 8501 patients in 20 countries participating in the international Dialysis Outcomes and Practice Patterns Study (DOPPS). All patients had been on HD therapy for longer than 120 days. The 4-month missed treatment rate varied from less than 1% in Italy and Japan to 24% in the United States.

After exclusion of patients from six countries with 4-month missed treatment rates of less than 5%, longitudinal and cross-sectional analyses were performed using data on 4493 patients. Potential predictors of missed HD treatments were analyzed, including country and patient and clinical variables.

On adjusted analysis, factors associated with a higher rate of missed treatments included younger age, shorter dialysis vintage, shorter prescribed HD treatment time, lower achieved Kt/V, more than 1-hour travel time to HD centers, and higher depression symptom score. The association with travel time was stronger in the United States: adjusted odds ratio 3.17, compared to 1.60 in other countries.

Patients with missed treatments were at increased risk of death from any cause: hazard ratio 1.68. Other adverse outcomes linked to missed HD sessions included death from cardiovascular causes, sudden death or cardiac arrest, hospital admission, serum phosphorus greater than 5.5 mg/dL, parathyroid hormone greater than 300 pg/mL, hemoglobin level less than 10 g/dL, higher perceived burden of kidney disease, and poorer general and mental health.

These findings add to previous evidence of poor outcomes among patients with missed HD sessions not due to hospitalization. Missed treatments may be a potentially modifiable factor to improve patient outcomes—particularly in the United States, which has the highest 4-month missed treatment rate of all DOPPS countries [Al Salmi I, et al. Missed hemodialysis treatments: international variation, predictors, and outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2018; 72:634–643].

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