ASN
KidneyNews
July 2018 | Vol. 10, Number 7

In Wake of Opioid Epidemic, Nephrologists Aim to Balance Pain Control, Safety in Patients

By Bridget M. Kuehn

More than 60% of dialysis patients had one or more prescriptions for a short course of opioid medications each year between 2006 and 2010, according to a recent analysis by scientists from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). About 20% of these patients had a prescription for a supply of 90 days or more of these medications.

The analysis, which used information from the U.S. Renal Data System on about 300,000 patients receiving dialysis with Medicare coverage, also found that both short-term and long-term use of opioids was associated with worse patient outcomes, including increased mortality, dialysis discontinuation, and hospitalization, according to lead author Paul Kimmel, MD, program director in NIDDK's Division of Kidney, Urologic, and Hematologic Diseases, and his colleagues.

"The only question is, are these drugs causing [poor outcomes] or are they a marker for poor health," Kimmel said in an interview. "Are patients who are sicker having more pain?"

The findings are the latest wrinkle in an ongoing debate about the use of opioids in medicine in the United States and how to balance the benefits of pain control with the risks associated with this class of drugs, including a growing epidemic of opioid abuse. For nephrologists, finding the right balance is a particularly delicate task. More than 50% of patients receiving dialysis report pain of varying degrees, which has been linked to greater depression and poorer quality of life, according to Kimmel and his colleagues. But safely and effectively treating pain in these patients, who are more vulnerable to adverse effects, is challenging.

"Patients with poor kidney function may be more prone to [opioid-related] drug toxicity compared to those with good kidney function," explained Phuong-Chi Pham, MD, chair of the division of nephrology at the Olive View–University of California Medical Center. "The increased toxicity may be due to reduced renal clearance, increased free drug levels, and/or increased volume of distribution and possibly increased tissue sensitivity to the same drug compared to patients without chronic kidney disease."

This leaves nephrologists with a difficult balancing act.

"We're responsible for optimizing their heath-related quality of life, minimizing their symptom burden; and part of that is understanding and treating them if they have substantial pain," said Sara Davison, MD, MSc, director of the Kidney Supportive Care Research Group at the University of Alberta in Canada. "We, as a community, need to commit to being able to do this in an effective manner, and that also means a safe manner."

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New Clue to Diabetic Nephropathy?

Podocyte Protein Linked to Hyperglycemia-Induced Kidney Damage in Mouse Model

By Tim O'Brien

Deficiency of protein tyrosine phosphatase 1B (PTP1B), specifically in podocytes, protects against hyperglycemia-induced renal damage in mice, according to a recent study in *Metabolism*.

The experimental study provides a tantalizing clue to the molecular mechanisms by which podocyte dysfunction leads to diabetic nephropathy—one of the most devastating complications of diabetes.

"We provide evidence of increased PTP1B expression in podocytes under high glucose," according to the research by Fawaz G. Haj, MSc, DPhil, of the University of California, Davis, and colleagues. "Also, podocyte-specific PTP1B disruption attenuated hyperglycemia-induced renal injury and preserved glucose control."

Haj and his colleagues performed a series of experiments to clarify the role of PTP1B in renal function. Previous

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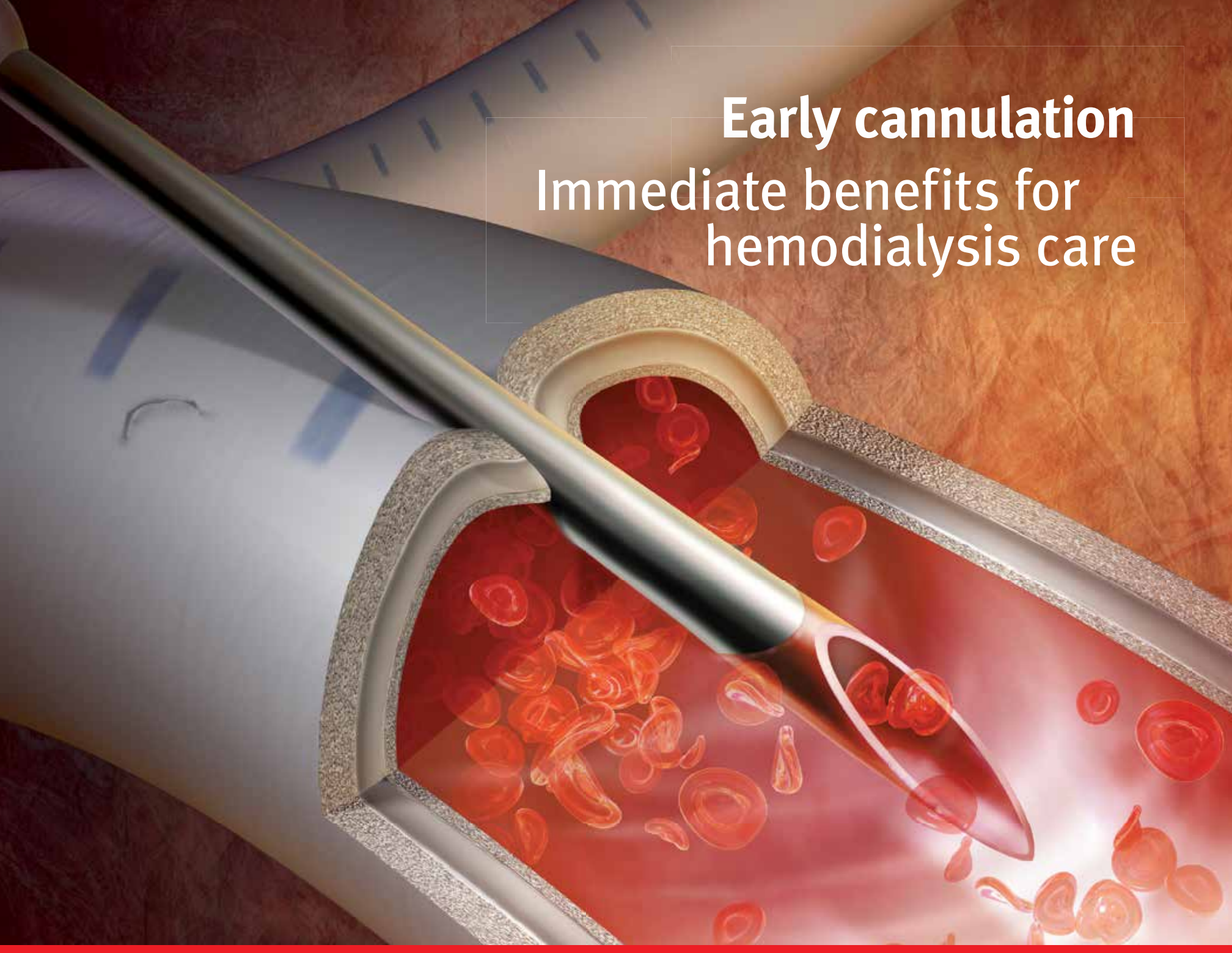

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Diabetic Nephropathy

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studies have established this enzyme as a metabolic regulator and a potentially important target for obesity and type 2 diabetes drugs. Studies in whole-body PTP1B knockout mice have shown improved insulin sensitivity, enhanced glucose tolerance, and resistance to obesity when the mice are fed a high-fat diet, which is associated with increased leptin signaling.

Studies using tissue-specific PTP1B disruption have shown distinct metabolic actions, including reduction in complement-mediated glomerular injury and protection against proteinuria. The new study examined the effects of PTP1B disruption in podocytes, which are believed to be involved in the pathogenesis of diabetic nephropathy.

Previous studies in rodents with podocyte injury have reported glomerular upregulation of PTP1B, particularly in podocytes.

Haj and colleagues generated mice with podocyte-specific PTP1B disruption, then compared the effects on renal function in normoglycemic animals versus those with hyperglycemia, induced either by a high-fat diet or by streptozocin. Both treatments led to increased expression of PTP1B by the kidneys. Disruption of podocyte-specific PTP1B in the presence of normoglycemia, however, did not affect renal function.

After induction of hyperglycemia, podocyte-specific PTP1B knockout mice did not show the signs of renal damage—including albuminuria, renal injury, and elevated serum glucose levels—observed in hyperglycemic control animals.

"Collectively, these findings demonstrate that podocyte PTP1B disruption protects renal function under streptozocin- and high-fat-diet–induced hyperglycemia and identify podocytes as contributors to the beneficial effects of PTP1B deficiency," the researchers write.

The reduction in hyperglycemia-induced renal injury was confirmed in histopathologic studies: animals with podocyte PTP1B disruption had less evidence of damage to podocyte structure and foot processes. Further experiments showed increased renal insulin signaling in podocyte PTP1B-knockout mice, along with decreased inflammation. Reductions in fibrosis, along with other findings, suggested that podocyte PTP1B disruption enhanced autophagy, an important regulator of kidney function and a suggested protective mechanism against podocyte injury.

In vitro studies in E11 "knockdown" mouse podocytes showed enhanced insulin signaling and autophagy in the presence of high glucose levels. These changes were reversed in cells with reconstituted expression of PTP1B. The protective effect of PTP1B deficiency against fibrosis was reduced in E11 cells treated with a pharmacologic knockdown inhibitor.

"Altogether, these data are in keeping with in vivo findings and are consistent with cell-autonomous effects that are due to PTP1B deficiency," the researchers said.

The findings lend potentially important new insights into the mechanisms of podocyte dysfunction and its contribution to the pathogenesis of diabetic nephropathy. In the presence of hyperglycemia, podocyte PTP1B expression is increased. Experimental disruption or deficiency of podocyte-specific PTP1B reduces hyperglycemia-induced renal injury while preserving glucose control.

These beneficial effects of podocyte PTP1B disruption are associated with improved insulin signaling and enhanced autophagy, with a likely causal relationship.

"These findings identify PTP1B in podocytes as a contributor to renal function under hyperglycemia," Haj and his colleagues conclude. They note their results are consistent with previous rodent models of podocyte injury, including reports that podocyte PTP1B disruption protects against glomerular and podocyte injury.

The unique contribution of the study is its focus on disruption of PTP1B in podocytes only, rather than the entire organism. In a press release, coauthor José Manuel Villalba of the University of Cordóba commented that PTP1B "is crucial in regulating the glucose metabolism. In certain circumstances, such as hyperglycemia, exclusive inhibition of the protein in podocytes will benefit the entire organism."

Could PTP1B and its substrates serve as therapeutic targets? Possibly, but as Vallalba notes, "There is still a lot of work to be done."

Because PTP1B is present throughout the body and serves a number of important functions, inhibition of this protein could have negative effects. However, if a drug could be developed that selectively inhibited PTP1B mainly in kidney cells, it might provide a new approach to treating or preventing diabetic nephropathy.

ASN KidneyNews

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ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

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Changes Under Consideration for Technical Expert Panels

The Senate Committee on Homeland Security and Governmental Affairs is reviewing a report and considering action to modify and expand requirements for federal advisory committees through the Federal Advisory Committee Act Amendments of 2017, H.R. 70.

At any given time, ASN members serve on multiple technical expert panels (TEPs) providing professional guidance to policymakers in the federal government, particularly the Department of Health and Human Services (HHS). TEPs and other federal advisory groups help inform public policy, and Congress has deemed it appropriate to require public transparency of advisory committee membership and activities.

However, TEPs are among the groups whose activities could be affected by the bill's amendments to the Federal Advisory Committee Act (FACA).

FACA defines a federal advisory committee as any term-limited committee, board, commission, council, conference, panel, task force, or similar group that dispenses objective advice and recommendations to officers and agencies of the executive branch, including TEPs commonly used by the Centers for Medicare & Medicaid Services.

In 1970, Congress conducted hearings that revealed the ways in which advisory committees were being used by agencies to cherry-pick industry leaders to advise on policy in secret. In addition, agencies did not have a standard set of requirements for advisory committee operations, resulting in uncontrolled costs, missing reports on activities, and duplication of roles between multiple committees.

As a result, Congress passed FACA in 1972 to give uniform guidance to agencies on how to operate advisory committees and report on their activities.

The current bill requires that appointments to federal advisory committees be made without regard to political affiliation or political activity, unless required by federal statute.

The head of a federal agency making an appointment to an advisory committee must give interested persons an opportunity to suggest potential committee members by including a request for comments in the Federal Register and providing a mechanism for interested persons to comment through the agency's official website. The agency must consider any comments submitted in making selections of advisory committee members.

The proposed bill requires that any individual appointed to an advisory committee who is not a full-time or permanent part-time officer or employee of the federal government shall be designated as:

(1) a special government employee if the individual is providing advice based on the individual's expertise or experience, or

(2) a representative if representing the views of an entity outside of the federal government.

Advisory requirements

The bill specifies that an agency may not designate committee members as representatives to avoid making them subject to federal ethics rules and requirements.

Also, a designated ethics official of each agency shall review the designation of each member of an advisory committee to determine whether such member's designation is appropriate and may redesignate members if appropriate.

The bill gives the Government Accountability Office the authority to review, and report on, compliance by agencies with FACA, including whether agencies are appropriately appointing advisory committee members as either special government employees or representatives.

The American Society of Nephrology (ASN) is monitoring this situation and any possible implications for ASN members.

Opioid Epidemic

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Too much or too little?

The use of opioids to treat pain, particularly chronic pain, has increased substantially in medicine in the United States since the late 1990s. But the practice has received growing scrutiny because of a parallel increase in opioid abuse and overdose deaths. These trends, along with regional variations in prescribing, "suggest inconsistent practice patterns and a lack of consensus about appropriate opioid use," according to a report from the U.S. Centers for Disease Control and Prevention (CDC).

Kimmel and his colleagues also found a substantial regional variation in rates of chronic opioid prescriptions for patients receiving dialysis, varying from 9.5% in Hawaii to 40.6% in West Virginia. More than one quarter of patients in Kimmel's study also received doses that were higher than those recommended by the CDC in a new guideline.

"Regional variations suggest that medical practice and social context is important in addition to patients' symptoms and diagnoses," Kimmel said.

Davison agreed that factors other than patient characteristics are likely driving the variation. "That suggests that there is some inappropriate prescribing, but there could be as much inappropriate overprescribing as underprescribing," she noted.

The United States as a whole prescribes far more opioids than the rest of the world, with use in the United States accounting for 80% of the world's supply although this country is home to only 5% of the world's population, according to a report from Express Scripts. The United States also consumes 99% of the world's hydrocodone. In fact, Kimmel's study found that the drugs most commonly prescribed for 90 days or more were hydrocodone and oxycodone.

"You're the only country that uses hydrocodone," Davison said. There are no data on the safety and effectiveness of hydrocodone in ESRD, so studies in the United States are needed, she said.

Data on the long-term use of opioids to treat pain in any patients are limited, with most studies lasting 12 weeks or less. A recent study published in the *Journal of the American Medical Association* found that the use of opioids versus nonopioid pain medications did not offer better pain-related function in patients with chronic knee or back pain at 12 months. There are no data on the long-term use of opioids in kidney disease that look at their effect on pain, function, cognition, quality of life, and adverse effects, Davison said. There is also little information on dosing in patients with kidney disease, she noted.

Pham expressed concern about the potential for adverse events associated with high dose and high potency opioids in patients with end stage renal disease (ESRD).

"The level of opioids prescribed among patients with ESRD is quite high and could be concerning among those who require high frequency and high doses of potent opioids," Pham said. "In particular, some patients with ESRD may have severe metabolic acidosis and rely on their intact respiratory drive to achieve optimal acid-base balance. High dose opioids may lead to reduced respiratory drive, concurrent respiratory acidosis, hence severe acidemia, which could lead to circulatory collapse and cardiac arrest."

Holistic approach

Experts in the field recommend that nephrologists take a holistic, stepwise, and multidisciplinary approach to treating pain in patients with kidney disease, reserving the use of opioids only when other options fail to provide relief.

Physicians should start with a thorough assessment of the pain, its cause, and whether it is reversible, according to an update on treatment of pain in chronic kidney disease by Pham and colleagues. For example, Kimmel noted that cramping and discomfort related to dialysis shouldn't be treated with opioids because they are unlikely to help. The same is true of neuropathic pain, which also doesn't respond well to most analgesics and would require very high doses of opioids, which would likely cause adverse effects, Davison said. For patients with musculoskeletal pain, early physical therapy with or without thermotherapy should always be encouraged, said Pham.

We're responsible for optimizing [patients'] heath-related quality of life, minimizing their symptom burden; and part of that is understanding and treating them if they have substantial pain.

Options for managing pain

Once the patient's pain has been assessed, physicians should discuss with them and their families their options for managing pain, Pham and colleagues wrote. When pain medications are necessary, physicians should follow the World Health Organization's three-step ladder approach, which starts with the use of nonopioid analgesics for mild pain; adds low-dose, lower-potency opioids to this regimen for moderate pain when needed; and reserves higher-dose or higher-potency opioids for patients who still require relief after the initial steps.

"In my opinion, opioids should only be given when the pain is obviously severe and cannot be treated by nonopioids or when patients have failed nonopioids such as acetaminophen, neuroleptics, or antidepressants whenever appropriate," said Pham.

Kimmel urged clinicians not to discount the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen in some patients with ESRD who are receiving dialysis. He and his colleagues found better outcomes in ESRD patients treated with NSAIDs than with opioids.

"We have to evaluate whether relatively safer drugs are underused in patients with end stage renal disease," he said. Nephrologists, he said, need to balance a potential loss of renal function with quality of life and other considerations. Davison said she typically reserves NSAIDs for patients with no residual renal function and limits their use to short periods of time.

A role for nondrug therapies

Kimmel, Pham, and Davison also recommended that nondrug therapies always be used alongside pain medication. These may include interventions like physical therapy, cognitive behavioral therapy, yoga, massage, or acupuncture.

"If we rely on medications alone we tend not to be successful," Davison said.

Kimmel and Davison recommended that nephrologists seek help from pain or palliative care specialists in managing chronic pain. "It has to be a medical community decision," Kimmel said. This is particularly important when pain management for patients with a history of substance use disorders is considered, noted Davison. In these cases, a pain specialist can provide close monitoring, develop adherence plans, and perhaps even dispense medications 1 week at a time, she noted.

Often, nephrologists may be seeing patients who have been prescribed pain medications for arthritis, postsurgical pain, or other types of pain by other physicians, noted Tess Novick, MD, a nephrology clinical fellow at Johns Hopkins University in Baltimore. But there's still a role for nephrologists in guiding pain care in these patients.

"We'd still be the ones helping the prescribers understand what their renal function is and if they should be adjusting the dose, like we do for all other medications," Novick said.

When opioids are chosen, Pham said, "always start with low-potency opioids at lowest dose and titrate up as needed." Patients should also be educated about adverse effects and the risk of opioid dependence, Pham said. Novick suggested also educating patients about the risk of overdose and the overdose antidote naloxone. The Substance Abuse and Mental Health Services Administration currently recommends that all patients prescribed chronic opioids have a prescription for naloxone as well, and provides information for physicians.

In the longer term, Kimmel would like to see clinical trials of drugs like buprenorphine, a partial opioid agonist also used in the treatment of opioid addiction, in patients with kidney disease to see whether it is a safer alternative. Kimmel also was optimistic about the future development of safer pain medications, including some nonaddictive treatments for chronic pain being studied at the National Institutes of Health.

Davison agreed on the need for more study.

"We need pragmatic clinical trials of multipronged approaches, of pain algorithms," she said. "We need to understand the effect of our approaches on the overall function of our patients. There's no point in treating pain effectively if we're causing patients to fall, we're causing them to have decreased cognition. We need to look at it holistically."

OPIOIDS **AND** KIDNEY DISEASES

Investigators Probe Kidney Effects of Opioid Abuse, Misuse

By Bridget M. Kuehn

An uptick of thrombotic microangiopathy (TMA) cases with a presentation similar to that of a rare blood disorder, thrombotic thrombocytopenic purpura, at Wake Forest Baptist Health in Winston-Salem, North Carolina, tipped off hematologist Peter Miller, MD, that something unusual was going on. An assistant professor at Wake Forest University, Miller had read a report from the U.S. Centers for Disease Control and Prevention (CDC) about similar cases linked to the illicit intravenous injection of a newly reformulated version of extended-release oxymorphone, Opana ER, so he and his colleagues began asking patients with suspected cases whether they had injected this oral medication.

"As soon as we did that, it was very evident we were on the verge of a crisis in our local area," Miller said.

North Carolina is one of many states grappling with an ongoing epidemic of opioid abuse and addiction. In 2017 alone, the state's emergency departments treated 5762 opioid overdoses—a 25.5% increase over the 4177 opioid overdose–related visits in 2016, according to the North Carolina Injury and Violence Prevention Branch. This mirrors a nationwide 30% increase in opioid overdose visits to emergency departments during that same period, according to the CDC.

For physicians like Miller and his colleagues, little data is available on the potential kidney risks associated with such opioid abuse, so they and other researchers have tried to fill the gaps. Some studies have found increased kidney risks associated with illicit opioid use, but how such use may harm the kidney isn't clear.

"It's still very much a black box," said Tess Novick, MD, a nephrology clinical fellow at Johns Hopkins University in Baltimore.

Kidney health and drug abuse

Before entering medical school, Novick was a social worker at a methadone clinic. Now she's interested in understanding whether or how prescription opioid and illicit drug use may affect kidney health.

"Kidney disease might be significantly impacted by both illicit and prescription drug use," Novick said.

In 2016, she and her colleagues published a prospective cohort study of 2286 people participating in the Healthy Aging in Neighborhoods of Diversity study, which found that lifetime use of opioids was associated with greater odds of a reduced estimated GFR (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.5–4.89) and a greater likelihood of albuminuria (OR 1.20, 95% CI 0.83–1.73). In that sample, about 15% of participants reported lifetime illicit use of opioids, including 13.6% who reported nonmedical use of prescription opioids and 1.8% who reported use of heroin.

"The opioid epidemic has gotten significantly worse since [those data were collected]," Novick said. "It was just starting to become an issue when we started looking at this."

Not all studies have found that increased risks to the kidney are associated with illicit drug use. But circumstances linked to inappropriate use of opioids, such as overdose-related dehydration, hypotension, rhabdomyolysis, and urine retention, can cause acute kidney injury (AKI), noted a recent review by Mary Mallappallil, MD, assistant professor at the State University of New York at Downstate Brooklyn, and colleagues.

Studying the health effects of illicit drug use is particularly challenging. Novick explained that studies often rely on self-reporting of drug use, which may not always be reliable. Changing patterns of substance abuse, including evolving methods of drug administration, varying drug formulations, adulterants, and often exposure to multiple toxins can make studying them a moving target that is hard to keep up with. For example, Mallappallil and her colleagues noted that cases of heroin-associated nephropathy, first described in the 1970s, appear to have been linked to adulterants.

Many basic questions still need to be answered about the potential kidney health effects of opioids themselves, including potential mechanisms of harm. Novick is now studying whether the risks associated with using opioid medications are different in patients with chronic kidney disease (CKD). She noted that many opioids are excreted by the kidney and that the drug's metabolism may be affected by poor kidney function, which might put patients at increased risk of opioid-related adverse events like overdose, death, central nervous system depression, or respiratory depression. "We don't know if the risk is different in patients with kidney disease, but theoretically they might be at increased risk because of their impaired ability to excrete these medications."

Mallapallil noted the importance of recognizing that changes in liver or kidney function can affect drug metabolism. Sometimes even physicians aren't aware that potential changes in drug metabolism may affect the safety of opioid medication use. She noted that there is evidence of medical misuse, leading to urine retention or rhabdomyolysis and eventually causing CKD.

"The liver and the kidney are the 2 main cleaning houses of toxins and medications," she said. "If both or one is affected to the point it could change drug metabolism, we assume that it may be okay, but it may not be."

AKI risks?

Many of the patients treated at Wake Forest after the intravenous abuse of extended-release oral oxymorphone received diagnoses of AKI, Miller said. So he and his colleagues followed up with an analysis of AKI in patients with a history of such use. They found that 47.8% of the 165 patients seen at Wake Forest in January 2012 and December 2015 with a history of such substance use had AKI. Most (59.4%) recovered from the kidney injury, but 13.9% experienced progression to ESRD, and 7.6% died at the hospital.

"We were able to determine that those that had the lowest degree of kidney injury tended to recover the most and the fastest," he said. "Those that had higher degrees of kidney injury had the lowest rate of recovery, and if they recovered, it took the longest."

The exact cause of the kidney injuries in these patients isn't clear. Many patients also had bacterial infections or were treated with drugs like vancomycin that can affect kidney function, Miller and his coauthors note. But a possible theory is that high-molecular-weight polyethylene oxide in the reformulated extended-release Opana may have contributed, Miller said. He collaborated on a study with U.S. Food and Drug Administration (FDA) scientists, which found that injecting guinea pigs with high-molecular-weight polyethylene oxide was associated with TMA and renal injury.

"We can't 100% say that is what it was, because it is likely multifactorial, but it seems to be something that is highly suspicious as the cause," Miller said.

In June 2017, the FDA requested that Opana ER be removed from the market, citing abuse-related concerns. One month later, the company voluntarily removed the product from the market while defending its risk–benefit profile.

"The abuse and manipulation of reformulated Opana ER by injection has resulted in a serious disease outbreak," said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research in a news release at the time. "When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market."

The consequences of intravenous abuse, or repeated abuse, of extended-release oxymorphone may not yet be completely evident with regard to kidney injury. Miller noted that some patients who experienced AKI may not be aware of it if they were not hospitalized.

Novick said that it's important for physicians to recognize that lifetime illicit drug use might be a risk factor for kidney disease. Miller noted that a history of intravenous drug use may also be a consideration in the creation of a permanent access for dialysis, which he and his colleagues worry could be used as a route of further abuse. To make sure patients receive appropriate and safe care, he said, it has become routine at his institution to ask patients throughout the hospital if they have a history of drug abuse.

"It's almost become second nature to ask almost every single patient," he said.

ASN, Peer Societies Advocate for Safe Alternatives to Manage Pain

By Rachel Shaffer and David White

Policymakers and public health officials are sounding the alarm about the opioid overdose crisis nationwide. More than 115 people die each day due to opioid-related drug overdoses, and the Department of Health and Human Services (HHS) Secretary Alex Azar has made combatting this epidemic one of his top priorities. White House and HHS officials have met with representatives of the American Society of Nephrology (ASN) and peer medical societies to discuss strategies to confront the epidemic and have also launched a public service campaign to help educate Americans about the highly addictive nature of opioids.

The Trump administration has launched the first phase of its long-promised anti-opioid media campaign as part of its efforts to address the opioid crisis. The first ads to run in the campaign target young adults, warning them of the dangers of opioid addiction. The ad campaign includes four television and digital ads featuring true stories of young people who have struggled with addiction and took steps to injure themselves in order to get access to more opioids.

"Many Americans have developed their addiction following treatment for a painful condition, and many are overdosing on prescription painkillers or illegal opioids like heroin and illicit fentanyl. In fact, it is estimated that between 60% and 75% of Americans who use heroin started with misusing prescription opioids," wrote Secretary Azar and Admiral Brett P. Giroir, MD, Assistant Secretary for Health, in a powerful public statement on the crisis released in June 2018 (1).

In addition to the public service campaign, one of the keys to success in reducing the fight against opioid-related deaths is ensuring patients and their families have access to safe alternatives to manage pain. ASN is working in partnership with other advocates in Washington—including the American Association of Kidney Patients (AAKP) and the Renal Physicians Association (RPA) to ensure alternatives exist for people affected by kidney diseases.

"But as we combat the opioid crisis, we cannot forget that pain is a real problem," wrote Giroir and HHS Secretary Azar in their statement. "Severe pain—chronic or acute—affects a broad spectrum of our fellow Americans: our children, our parents, our spouses, our relatives, or our neighbors. We must do a better job of securing for them safe, effective options for managing pain."

Pain and pallliative care

The increased national focus on the potential dangers of opioid products also comes at a time of increased national focus on the importance of palliative care throughout the course of patients' lives—not just when the conservative care option is selected—and recognizing pain management as an important part of quality of life from the patient perspective.

For people with kidney diseases, however, finding the right pain management solution can be complicated by the importance of avoiding non-steroidal anti-inflammatory drugs (NSAIDS), which can harm the kidneys and hasten the progression to kidney failure. As our nation's healthcare system aims to reduce misuse of opioids, safe alternatives such as over-the-counter medications like acetaminophen become important tools in the toolbox, especially for people for whom NSAIDS are unsafe.

"Concerningly, the Food and Drug Administration issued notice under the Obama administration that it planned to limit access to higher-strength acetaminophen, which can be obtained over the counter," commented ASN President Mark D. Okusa, MD, FASN. "For people with kidney diseases, especially those who already face a high daily pill burden, limiting access to higher-dose acetaminophen products would present a challenge. They may either be forced to increase pill burden with multiple lower doses of the product, or consider more risky pain management strategies such as NSAIDS or even opioids."

At a time when safer alternatives to opioids are needed, ASN and other members of the Patient Access to Pain Relief coalition are advocating to ensure that access to acetaminophen—which when used appropriately constitutes a safe pain management option—is preserved under the Trump administration.

In June 2018, HHS hosted the first meeting of the Pain Management Best Practices Inter-Agency Task Force, a critical component of the 2016 Comprehensive Addiction and Recovery Act. This important body is charged with reviewing current best practices, determining if there are any gaps in practice, and developing recommendations to improve pain management.

The Task Force includes representatives of HHS agencies, the VA, Department of Defense, and the Office of National Drug Control Policy, as well as non-federal representatives with diverse expertise in pain management, advocacy, addiction, recovery, substance use disorders, mental health, minority health, and more. Members also include patients, first responders, hospitals, and groups with expertise in overdose reversal.

In recent weeks, the society and other coalition members have met with both White House staff and top HHS aides, focusing on the need to educate about safe use of acetaminophen instead of restricting access to it altogether.

ASN will continue to work collaboratively to ensure people with kidney diseases and their care teams have access to a range of safe alternatives to opioids and NSAIDS.

Reference

1. https://www.hhs.gov/blog/2018/06/01/dont-forget-those-who-are-suffering-from-pain.html

Opioid legislation includes slew of provisions to curb misuse

By David White

When *Kidney News* went to print, the U.S. House of Representatives had passed H.R. 6, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. Passed with bipartisan support, H.R. 6 combines provisions from more than 50 bills approved individually by the House.

The bill is designed to help overall efforts to combat the opioid crisis by advancing treatment and recovery initiatives, bolstering prevention efforts, and trying to counter deadly illicit synthetic drugs like fentanyl.

A last-minute addition to the legislative package in the House would extend by three months the period people with chronic kidney failure must wait before they become eligible for Medicare coverage. Lawmakers inserted the change—which is projected to save the government $290 million over a decade—to help pay for their slew of new initiatives aimed at curbing opioid misuse. The bill passed the House by a vote of 396–14.

The bill then headed to the Senate, where lawmakers were planning to take up their own opioid legislation. At press time, a House Republican aide said leadership hopes to conference the bills in July, although it could slide later into the summer depending on the Senate's schedule. Senate Health, Education, Labor and Pensions Committee Chair Lamar Alexander (R–TN) is leading efforts to combine bills from his committee and the Senate Finance and Judiciary committees into a package that would go to the Senate floor.

Here are the major provisions of the legislation.

Medicaid

- Require state Medicaid programs to not terminate a juvenile's medical assistance eligibility because the juvenile is incarcerated. A state may suspend coverage while the juvenile is an inmate, but must restore coverage upon release without requiring a new application unless the individual no longer meets the eligibility requirements for medical assistance (H.R. 1925)
- Enable former foster youth who are in care by their 18th birthday and previously enrolled in Medicaid to receive health care until the age of 26 if they move out of state (H.R. 4998)
- Require the Centers for Medicare & Medicaid Services (CMS) to carry out a demonstration project to provide an enhanced federal matching rate for state Medicaid expenditures related to the expansion of substance-use treatment and recovery services targeting provider capacity (H.R. 5477)
- Require all state Medicaid programs to have a beneficiary assignment program that identifies Medicaid beneficiaries at risk for substance use disorder (SUD) and assigns them to a pharmaceutical home program, which must set reasonable limits on the number of prescribers and dispensers that beneficiaries may utilize (H.R. 5808)
- Require state Medicaid programs to have safety edits in place for opioid refills, monitor concurrent prescribing of opioids and certain other drugs, and monitor antipsychotic prescribing for children (H.R. 5799)
- Require CMS to issue guidance on Neonatal Abstinence Syndrome (NAS) treatment options under Medicaid and require a study by the nonpartisan Government Accountability Office (GAO) on coverage gaps for pregnant women with SUD (H.R. 5789)
- Provide additional incentives for Medicaid health homes for patients with substance use disorder (H.R. 5810)

Medicare

- Instruct CMS to evaluate the utilization of telehealth services in treating SUD (H.R. 5603)
- Create a pass-through payment extension under Medicare to encourage the development of non-opioid drugs (H.R. 5809)
- Add a review of current opioid prescriptions and, as appropriate, a screening for opioid use disorder (OUD) as part of the Welcome to Medicare initial examination (H.R. 5798)
- Incentivize post-surgical injections as a pain treatment alternative to opioids by reversing a reimbursement cut for these treatments in the Ambulatory Service Center setting, as well as collect data on a subset of codes related to these treatments (H.R. 5804)
- Require e-prescribing, with exceptions, for coverage of prescription drugs that are controlled substances under the Medicare Part D program (H.R. 3528)
- Require prescription drug plan sponsors under the Medicare program to establish drug management programs for at-risk beneficiaries (H.R. 5675)
- Provide access to Medication-Assisted Treatment (MAT) in Medicare through bundled payments made to Opioid Treatment Programs for holistic service (Section 2 of H.R. 5776)

Public health

- Direct the Food and Drug Administration (FDA) to issue or update guidance on ways existing pathways can be used to bring novel non-addictive treatments for pain and addiction to patients. (H.R. 5806)
- Authorize grants to state and local agencies for the establishment or operation of public health laboratories to detect fentanyl, its analogues, and other synthetic opioids (H.R. 5580)
- Make the buprenorphine prescribing authority for physician assistants and nurse practitioners permanent. Temporarily allow advanced practice registered nurses to prescribe buprenorphine. In addition, H.R. 6 will permit a waivered-practitioner to immediately start treating 100 patients at a time with buprenorphine (skipping the initial 30 patient cap) if the practitioner has board certification in addiction medicine or addiction psychiatry; or if practitioner provides MAT in a qualified practice setting.

Policy Update

CMS to Focus on Data Reporting and Monitoring, Prevention, and Treatment to Address Opioid Crisis

The Centers for Medicare & Medicaid Services (CMS) released the "CMS Roadmap to Address the Opioid Epidemic" in June 2018 (1). CMS stated at the time that "although some progress has been made in efforts to combat the opioid epidemic, the latest data from the Centers for Disease Control and Prevention (CDC) indicate the crisis is not slowing down" (2).

Highlights of the crisis are:

- Opioids killed more than 42,000 people in the United States in 2016 or 116 people a day.
- 40% of all opioid overdose deaths involve a prescription opioid.
- 11.5 million people misused prescription opioids at the same time.
- 3 out of 4 people who used heroin misused prescription opioids first.

As part of the roadmap, CMS details its three-pronged approach to combating the opioid epidemic:

- Prevention of new cases of opioid use disorder.
- Treatment of patients who have already become dependent on or addicted to opioids.
- Utilization of data from across the country to target prevention and treatment activities.

Current estimates show that over 2 million people suffer from opioid use disorder, with a prevalence in Medicare of 6 out of every 1000 beneficiaries. In order to decrease that number, CMS believes it is crucial that Medicare beneficiaries and providers are aware that there are options available both to help prevent the development of new cases of opioid use disorder and to help treat existing cases. CMS stated it wants to ensure that beneficiaries are not inadvertently put at risk of misuse by closely monitoring prescription opioid trends, strengthening controls at the time of opioid prescriptions, and encouraging healthcare providers to promote a range of safe and effective pain treatments, including alternatives to opioids.

CMS outlined some clear steps and objectives in the three areas outlined in its Roadmap.

Prevention

- Implementing a new authority to limit Medicare beneficiaries to certain pharmacies and doctors (or "lock-in").
- Strengthening real-time prescription controls with the use of prescription databases and point of sale pharmacy edits.
- Establishing other standard pharmacy protocols across programs for new or changed prescriptions.

Additionally, CMS would like to 1) **incorporate incentives for appropriate prescribing** into future Medicare Quality Star Ratings and the Quality Payment Program; 2) **align monitoring of systemic overprescribing** to CDC guidelines and partner with law enforcement to stop egregious prescribing; 3) **disseminate best practices** for state Medicaid agencies and other payers on alternative pain management strategies and other tactics to address the opioid crisis.

Treatment

CMS plans to address these areas in order to identify and develop solutions for treatment barriers for pain and opioid use disorders across Medicare, Medicaid, and private health plans:

- Access to non-opioid pain treatments,
- Access to medication-assisted treatments, and
- Access to providers in rural and other low-access communities.

Data

In order to focus its data efforts and provide tools for states, plans, and providers, CMS will address these areas:

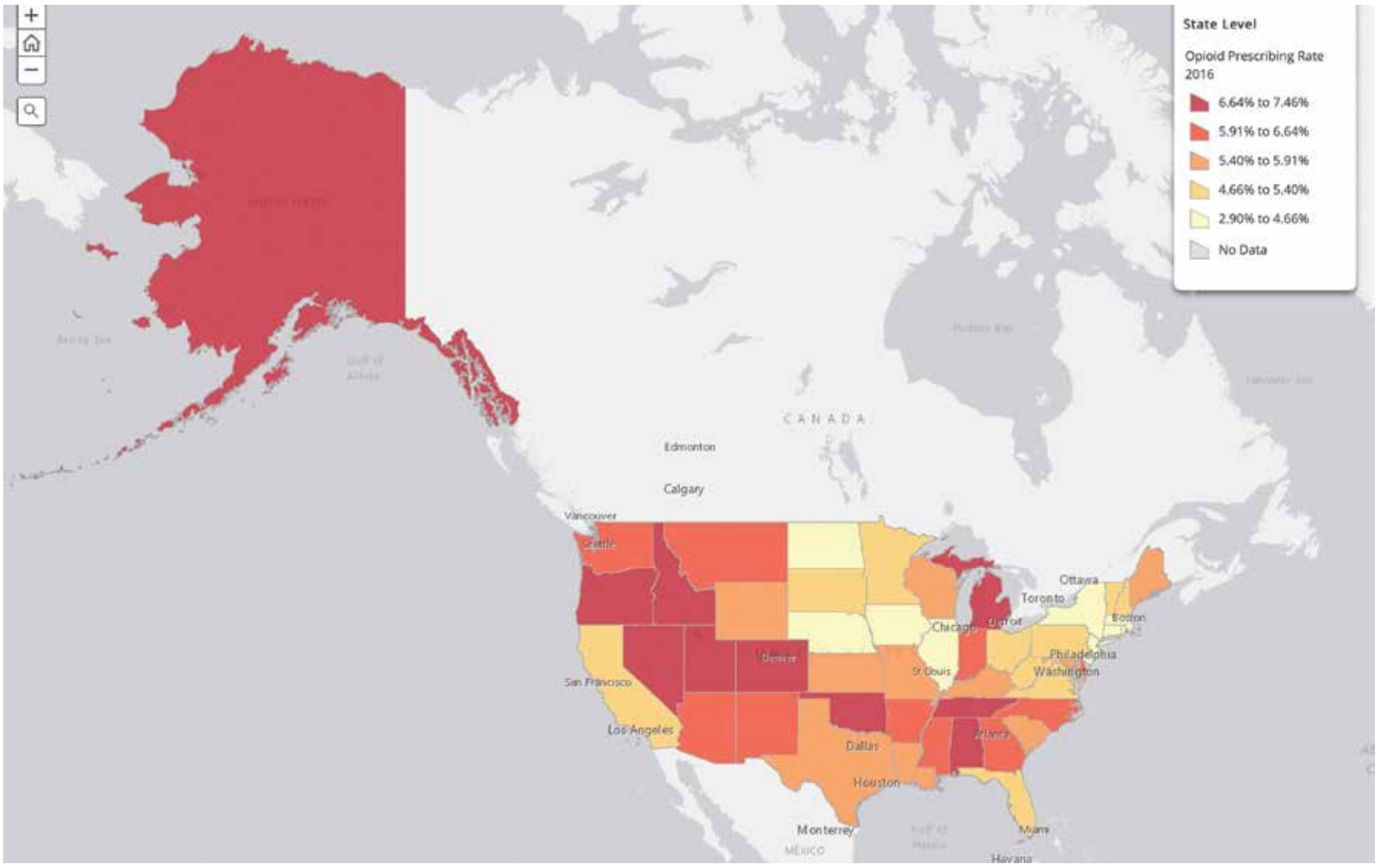
- **Monitoring** the success of prevention measures related to reducing overuse and misuse of prescription opioids.
- **Improving** data transparency and interoperability and expanding tools like the Medicare "heat map" of prescribing rates that help determine where to target safe prescribing efforts (Figure 1).
- **Analyzing** prescription opioid use patterns across CMS programs and in special populations such as individuals in rural areas, with dual Medicare/Medicaid eligibility, and with certain health conditions.
- **Supporting** state Medicaid programs' capacity to track and report data.

Kidney News will continue monitoring and reporting further developments in opioid-related policy.

References

1. https://www.cms.gov/About-CMS/Agency-Information/Emergency/Downloads/Opioid-epidemic-roadmap.pdf
2. https://blog.cms.gov/2018/06/11/cms-opioids-roadmap/

Figure 1. Opioid prescribing under Medicare Part D by state, 2016



Courtesy Centers for Medicare & Medicaid Services

Illicit Drug Use Linked with Disease Progression and Early Death in Kidney Disease Patients

Adding to previous studies suggesting that illicit drug use is associated with the development of chronic kidney disease (CKD), new research indicates that it may also put patients with established CKD at elevated risk of disease progression and early death.

In the *Clinical Journal of the American Society of Nephrology* study, researchers assessed whether behavioral risk factors—including tobacco, alcohol, and illicit drug use, all of which may exhibit direct or indirect nephrotoxic effects—have an impact on the outcomes of patients with CKD.

They found that persistent use of hard illicit drugs was linked with a 25% higher risk for CKD progression and a 41% higher risk of dying compared with non-use of drugs.

For their analysis, the investigators examined information from the Chronic Renal Insufficiency Cohort Study, a prospective longitudinal cohort study including 3939 participants with CKD in the United States. Self-reported information on tobacco smoking, alcohol drinking, marijuana use, and hard illicit drug (cocaine, heroin, or methamphetamine) use was obtained at the start of the study and at annual follow-up visits.

"We hypothesized that each of the substances would be associated with higher risk of both CKD progression and death. Our hope was to identify important and preventable lifestyle risk factors implicated in the progression of CKD and death among patients with CKD," said senior author Jiang He, MD, PhD, Chair of Epidemiology at Tulane University School of Public Health and Tropical Medicine.

The team modeled substance use exposures using 3 approaches: baseline time-fixed exposure, time-updated most-recent exposure, and time-updated cumulative average exposure.

Over a median follow-up of 5.5 years, 1287 participants experienced CKD progression and 1001 died. Baseline proportions of hard illicit drug use, tobacco smoking, alcohol drinking, and marijuana use were 12%, 13%, 20%, and 33%, respectively. Compared with non-use of hard illicit drugs throughout follow-up, persistent drug use was linked with a 25% higher risk for CKD progression and a 41% higher risk of premature death.

The other factors did not have significant associations with CKD progression, although persistent tobacco smoking was linked with an 86% higher risk of dying, while persistent alcohol drinking was linked with a 27% lower risk of dying. Compared with non-use of marijuana throughout follow-up, persistent marijuana use was not significantly linked with risk of CKD progression or dying.

"The US is in the midst of an opioid epidemic, which has led to increases in the use and abuse of heroin. Additionally, efforts for the decriminalization and legalization of illicit drugs, especially marijuana, are gaining traction—for example, more than half of US states currently allow medicinal and/or recreational use of marijuana," He said. "It is important to try to quantify the long-term health consequences of substance use, especially among vulnerable populations such as patients with chronic conditions like CKD, who are at high risk for poor health outcomes."

Contaminants a consideration?

Additional research is needed to determine how illicit drugs may affect kidney health.

The authors note that nephropathies of varying etiology—including glomerulonephritis, secondary amyloidosis, and heroin-specific nephrotic syndrome—are associated with heroin use, yet the incidence of heroin nephropathy has declined despite an increase in prevalence of heroin abuse.

Leal Herlitz, MD, Director of Medical Kidney Pathology at the Cleveland Clinic, noted that it will be important to consider the possibility that contaminants or other factors associated with consumption of these drugs are the driving factors behind the increased risk of CKD progression and mortality.

Herlitz, who was not involved in the study, also stressed that until this research was published, there was virtually nothing but anecdotal evidence regarding risk of CKD and use of marijuana or hard illicit drugs.

"It is notable that a third of respondents reported marijuana use . . . and that there was no increased risk for either CKD progression or all-cause mortality with marijuana use," she said. "This is important information to have as marijuana is increasingly legal in the United States and it is likely that nephrologists will be seeing increasing numbers of patients who engage in either recreational or medical use marijuana. This study would suggest that marijuana use is far less dangerous to our patients than use of tobacco, cocaine, or heroin."

Concerning alcohol, the protective effect on mortality may relate to the postulated cardioprotective effects of mild to moderate alcohol consumption.

"With the low proportion of patients reporting alcohol use, this study was not able to refine the difference between patients who engage in heavy alcohol consumption with either moderate or mild consumption," Herlitz said.

Finally, not surprisingly, this study adds to the evidence that continued tobacco use is bad for your health.

"An increased risk of CKD progression was not found [for tobacco use], though this may be due to the relatively small proportion of patients who reported ongoing tobacco use and the fact that the increased mortality risk may eclipse the progression of CKD," Herlitz noted.

Cognitive Impairment Affects Transitions from CKD to ESRD Care

One out of every five patients with non–dialysis-dependent CKD has some form of cognitive impairment. A new study finds that these individuals may experience important differences in their transition to dialysis compared with patients without cognitive impairment.

Patients with advanced CKD are at risk for cognitive impairment, which is commonly underdiagnosed in clinical practice. It is unknown how cognitive deficits may affect planning and preparation for progression to ESRD, so the authors of the *American Journal of Kidney Diseases* study set out to investigate.

The retrospective study included 630 patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. The patients underwent cognitive assessment during late-stage chronic kidney disease (CKD), defined as an estimated glomerular filtration rate of 20 mL/min/1.73 m^2 or less. They later initiated maintenance dialysis therapy.

Nineteen percent of patients met study criteria for predialysis cognitive impairment, which was defined as a Modified Mini-Mental State Examination (3MS) score less than previously defined thresholds for age. Associations with cognitive impairment were assessed for four patient outcomes: peritoneal dialysis (PD) as initial modality, preemptive permanent access placement, venous catheter avoidance at dialysis initiation, and preemptive waitlisting for a kidney transplant.

Overall, 16% of patients had PD as their initial modality, 75% had preemptive access placement, 45% avoided venous catheter use at dialysis initiation, and 20% were preemptively waitlisted for kidney transplantation.

The investigators found that predialysis cognitive impairment was independently associated with a lower likelihood of two of the four outcomes on adjusted analysis. Adjusted odds ratios were 0.22 for PD as initial modality and 0.58 for catheter avoidance at dialysis initiation. There was no significant difference in preemptive permanent access placement or venous catheter avoidance at dialysis initiation.

On analysis using a threshold 3MS score of less than 80, predialysis cognitive impairment was present in 14% of patients. Initial associations with all four outcomes became nonsignificant on adjusted analysis.

These CRIC Study data suggest that a substantial proportion of patients with advanced CKD have predialysis cognitive impairment. Such patients have lower use of initial PD therapy and higher use of venous catheters at dialysis initiation.

"Typical approaches to ESRD preparation, which rely heavily on patients to drive the process forward, may not be equally effective for patients with cognitive impairment," the researchers write. They call for further study of interventions to mitigate the effects of cognitive impairment on the transition to ESRD.

Harhay MN, et al. Cognitive impairment in non–dialysis-dependent CKD and the transition to dialysis: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2018; DOI: 10.1053/ j.ajkd.2018.02.361.

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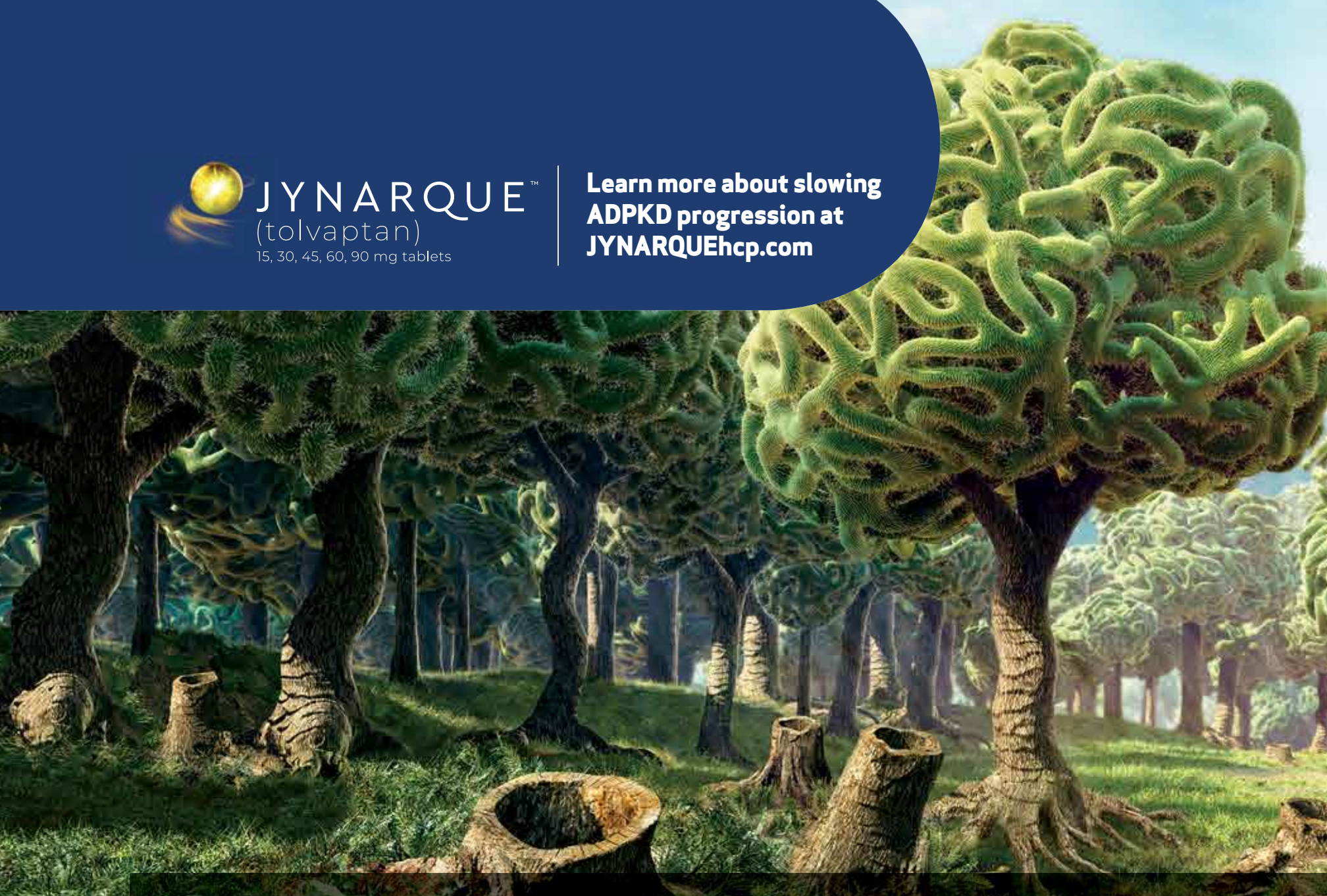

INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE™ (tolvaptan)

INDICATION:
JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

HELP CONSERVE NEPHRON FUNCTION BY SLOWING THE DECLINE OF KIDNEY FUNCTION WITH THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR ADPKD

JYNARQUE™ (tolvaptan) slows disease progression, so you can finally take a stand against ADPKD

ADPKD=autosomal dominant polycystic kidney disease.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **OATP1B1/3 and OAT3 Transporter Substrates:** Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- **BCRP Transporter Substrates:** Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin)
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist.

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including **BOXED WARNING**, on the following pages.

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June 2018 10US18EBP0160

How Much Faster Does Renal Function Decline in People with Diabetes?

Kidney function declines twice as rapidly in adults with versus without diabetes, according to a population-based study in *Diabetes Care*.

The study used data on 15,517 racially diverse participants enrolled in the Atherosclerosis Risk in Communities study, with four study visits between 1987 and 1989 and 2011 to 2013. At baseline, 88% of participants were free of diabetes, 4% had undiagnosed diabetes, and 8% had diagnosed diabetes. Those in the two diabetes groups were older, more likely to be black, more likely to have hypertension and coronary heart disease, had a higher mean body mass index, and had a lower mean high-density lipoprotein cholesterol. Serial eGFR measurements over 26 years of follow-up were analyzed to characterize patterns of diabetes-related eGFR decline, along with risk factors associated with more rapid decline in kidney function.

On adjusted analysis, eGFR declined by a mean of –1.4 mL/min/1.73 m^2/year in participants without diabetes compared to –1.8 mL/min/1.73 m^2/year in those with undiagnosed diabetes and –2.5 mL/min/1.73 m^2/year in those with diagnosed diabetes. The more rapid eGFR decline in the diabetic groups remained significant after adjustment for diabetes- and kidney disease–related risk factors. In the diagnosed diabetes group, factors associated with more rapid eGFR decline were African American race, APOL1 high-risk genotype, systolic blood pressure 140 mm Hg or higher, insulin treatment, and higher glycated hemoglobin.

Diabetes may contribute to about half of cases of ESRD, but relatively little is known about patterns of decline in kidney function before the development of advanced kidney disease. These community-based data confirm that diabetes is a major risk factor for decline in kidney function, with declines in eGFR occurring nearly twice as fast as in adults without diabetes. The study identifies potentially modifiable risk factors for diabetes-related decline in kidney function, particularly hypertension and glycemic control [Warren B, et al. Diabetes and trajectories of estimated glomerular filtration rate: a prospective cohort analysis of the Atherosclerosis Risk in Communities Study. *Diab Care* 2018; https://doi.org/10.2337/dc18-0277].

New Score Allows Early Prediction of AMI Readmission Risk

A new "AMI READMITS" score—based on renal function, diabetes, and low blood pressure, among other factors in the first 24 hours in the hospital—identifies patients at high risk of readmission after acute myocardial infarction, reports a study in the open-access *Journal of the American Heart Association*.

Using data from consecutive AMI hospitalizations to six diverse Texas hospitals in 2009–2010, the researchers sought to develop a pragmatic model to predict the risk of all-cause, nonelective hospital readmission within 30 days. The model was derived using data on 826 patients, 13% of whom were readmitted within 30 days. Two separate AMI-specific models were developed and evaluated: a "first-day" model using only data from the first 24 hours in the hospital and a "full-stay" model including data from the full hospital stay.

The first-day model, called AMI READMITS, consisted of seven predictors: renal function (serum creatinine greater than 2 mg/dL), elevated brain natriuretic peptide, age, history of diabetes, nonmale sex, absence of timely percutaneous coronary intervention; and systolic blood pressure less than 100 mm Hg. This score provided good discrimination, C-statistic 0.75, and identified a broad range of risk categories, with average risks of 2.1% to 41.1% by decile. About one-third of patients classified as high risk (AMI READMITS score 20 or higher) had 30-day readmission, compared to 2% of those classified as low risk (score 13 or lower).

The full-stay model added three further predictors: intravenous diuretic use, anemia at discharge, and discharge to postacute care. However, it provided minimal net reclassification improvement and calibration. Both models appeared to have better performance compared to other models.

Readmission after AMI is a common problem, but current models have modest predictive value and do not provide readily actionable data to reduce risk. The new AMI READMITS score is a parsimonious model that includes clinically relevant risk factors and provides actionable data to identify patients at high risk of readmission during their first 24 hours in the hospital. The researchers note, "[C]linical severity measures directly related to the AMI (shock, heart strain or failure, renal dysfunction) and timely percutaneous coronary intervention were strong predictors of readmission risk" [Nguyen OK, et al. Predicting 30-day hospital readmissions in acute myocardial infarction: the AMI "READMITS" (renal function, elevated brain natriuretic peptide, age, diabetes mellitus, nonmale sex, intervention with timely percutaneous coronary intervention, and low systolic blood pressure) score. *J Am Heart Assoc* 2018; 7:e008882. DOI: 10.1161/JAHA.118.008882].

Renal Denervation for Persistent Hypertension on Medications: Randomized Trial

Renal denervation safely reduces blood pressure in patients with uncontrolled hypertension who continue taking antihypertensive medications, reports a trial in *The Lancet*.

The SPYRAL HTN-ON MED trial enrolled 487 adults with uncontrolled hypertension at 25 centers in Asia, Australia, Europe, and North America. All had uncontrolled hypertension, including an ambulatory systolic BP of 140 to 170 mm Hg despite at least 6 weeks on stable doses of one to three antihypertensive medications. After renal angiography, patients were randomly assigned to catheter-based renal denervation of the main renal arteries and branches or a sham procedure with sensory masking. All procedures were performed by an experienced proceduralist following a detailed treatment plan.

At follow-up visits, patients underwent 24-hour ambulatory BP monitoring, as well as urine and blood tests to assess adherence to prescribed medications. The current paper presents a proof-of-concept analysis of the first 80 patients treated: 38 assigned to renal denervation and 42 to the sham control procedure. The main efficacy outcome was change in ambulatory BP from baseline to 6 months, with a prespecified requirement for the patient to remain on the same antihypertensive drug regimen during this time. Major

Continued on page 18 >

Findings

Continued from page 17

adverse events included death, ESRD, and renal artery stenosis.

The two groups had similar baseline characteristics; just over half of patients were taking three classes of antihypertensive medications. Mean 24-hour ambulatory BP was 152.1/97.2 mm Hg in the renal denervation group and 151.3/97.9 mm Hg in the sham control group.

At 6 months, the renal denervation group had significant reductions in BP measurements. Mean baseline-adjusted treatment differences in 24-hour BP were –7.0 mm Hg systolic and –4.3 mm Hg diastolic. For office BP, the differences were –6.6 and –4.2 mm Hg, respectively. Compared to the sham group, the difference in the renal denervation group was –7.4/–4.1 mm Hg for 24-hour BP and –6.8/–3.5 mm Hg for office BP.

Analysis of hourly data showed significant reductions in BP throughout the 24-hour monitoring period in patients assigned to renal denervation. The between-group differences in BP were not significant at 3 months' follow-up. Laboratory tests showed medication adherence of about 60%, with significant variation for individual patients throughout the study. No patient in either group experienced major adverse events.

Previous studies of renal denervation for treatment of hypertension have yielded conflicting results. The recent SPYRAL HTN-OFF MED trial showed "significant and meaningful" reductions in BP in the absence of antihypertensive medications. The SPYRAL HTN-ON MED study evaluated the outcomes of renal denervation in a clinically representative situation in which this procedural approach might be integrated with continued antihypertensive drug treatment.

The results show greater reductions in BP with renal denervation compared to a sham procedure in patients with uncontrolled hypertension who continue taking antihypertensive drugs. The authors note that about half of patients did not follow their prescribed antihypertensive regimen during follow-up, even though they were aware that adherence would be monitored as part of the study [Kandzari DE, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; https://doi.org/10.1016/S0140-6736(18)30951-6].

Metformin Appears Safe for Most Diabetics with CKD

The oral antidiabetic drug metformin does not increase the risk of hospitalization for acidosis in patients with mild to moderate CKD, according to a "real world" study in *JAMA Internal Medicine*.

The community-based cohort study included 75,413 patients with type 2 diabetes in a large regional healthcare system who had serum creatinine measurements between 2004 and 2017. Metformin use and dose were analyzed for association with hospital admission for acidosis, accounting for time-related changes in eGFR. The study included replication in a sample of 67,578 new metformin users and 14,439 new sulfonylurea users, drawn from an individual-level inpatient and outpatient claims database.

The healthcare system cohort was 51% female, with a mean age of 60.4 years. At a median 5.7 years' follow-up, there were 2335 hospitalizations with acidosis. Of these, only 29 had acidosis as the primary diagnostic code.

Overall, there was no significant association between time-dependent metformin use and incident acidosis, compared to alternative diabetes treatment. The risk of acidosis increased along with eGFR. However, the association became significant only at an eGFR of less than 30 mL/min/1.73 m^2: adjusted hazard ratio 2.07. The association remained significant after adjustment for time-dependent use of a wide range of other medications. Lower eGFR was associated with a higher incidence of acidosis, whether or not the patients were using metformin.

The results were similar on analysis of new metformin versus sulfonylurea users, in a propensity-matched cohort, and on analysis excluding patients using insulin at baseline. In the replication analysis, there was no significant difference in acidosis risk for metformin versus sulfonylurea users, even at eGFR values less than 30 mL/min/1.73 m^2.

About 20% of patients with type 2 diabetes have an eGFR of less than 60 mL/min/1.73 m^2. Metformin is the first-line treatment for type 2 diabetes. However, it may be avoided in diabetic patients with CKD due to concerns about drug accumulation and lactic acidosis.

The new study, based on extensive data from two real-world settings, finds no association between metformin and incident acidosis in patients with type 2 diabetes and eGFR of 30 to 60 mL/min/1.73 m^2. Metformin appears to increase acidosis risk only for diabetic patients with eGFR of less than 30 mL/min/1.73 m^2. The researchers write, "From a public health perspective, the potential benefits of using metformin for patients with [diabetes] and CKD are vast, given the increasing number of people affected with both diseases worldwide" [Lazarus BN, et al. Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. *JAMA Intern Med* 2018; DOI:10.1001/jamainternmed.2018.0292].

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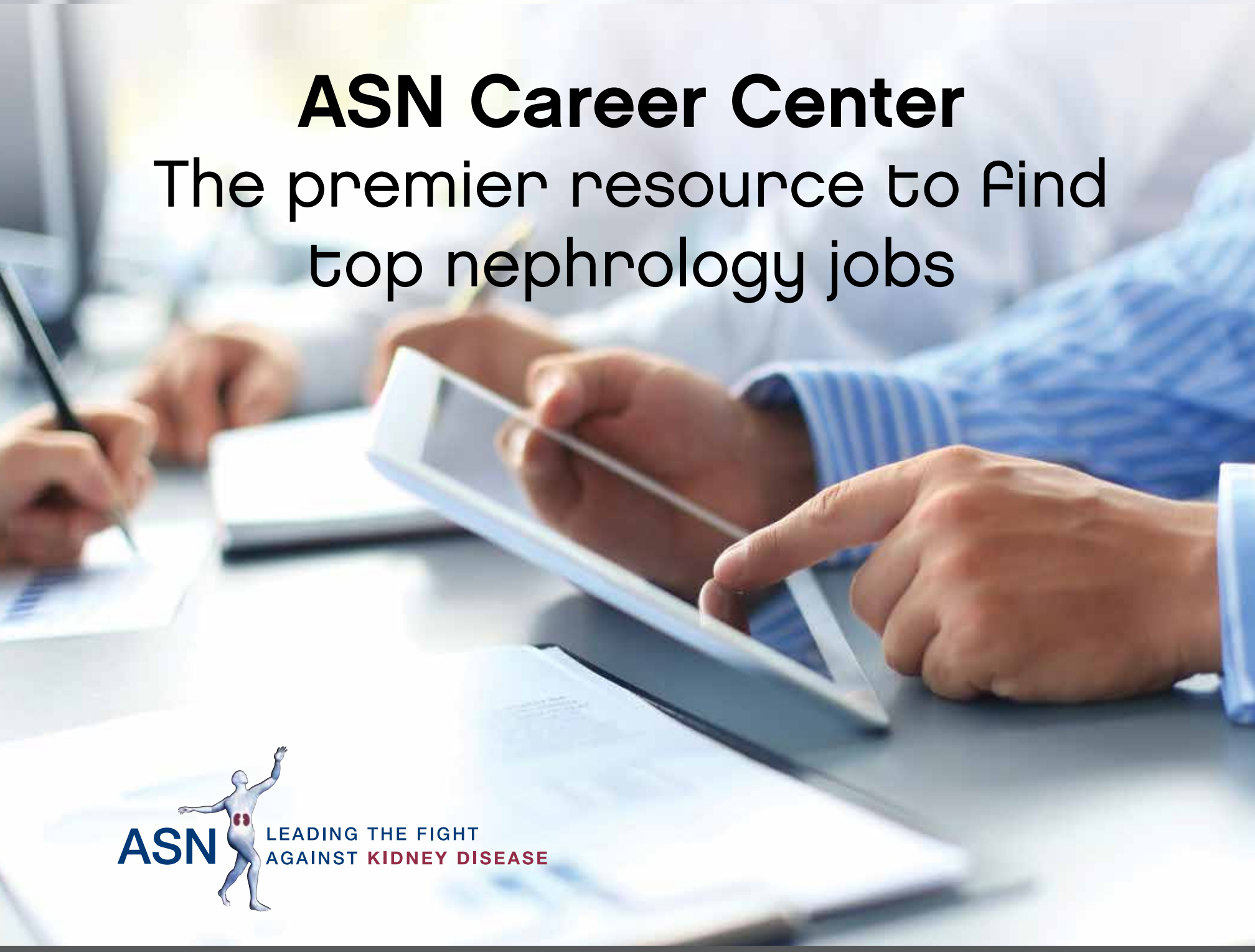

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FDA Approval of Tolvaptan for PKD: Breakthrough Therapy vs. Value-Based Care

By Richard Lafayette

Richard Lafayette, MD

In April 2018, the U.S. Food and Drug Administration (FDA) approved the use of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (PKD), allowing the United States to join most of the rest of the world in having the ability to deploy the first disease-specific therapy for PKD. Approval followed the release of results of the REPRISE trial, which demonstrated tolvaptan's ability to meaningfully slow progression of stage 3 and 4 CKD over 12 months compared to placebo (1). The REPRISE study validated the results of the TEMPO trial, which initially provided strong evidence that tolvaptan could slow the progression of kidney cyst growth and preserve kidney function (2).

Together, the studies suggest that tolvaptan can slow GFR loss by 1–1.5 mL/min/1.73 m^2 per year (slowing rates by 20% to 30%), enough to extend independent kidney function by many years. These studies strongly suggest a clinically meaningful ability of tolvaptan to improve quality of life by delaying cyst growth (less back pain and kidney pain—but more fatigue and gastrointestinal symptoms), and through slowing decline in renal function, to delay the need for kidney transplantation and/or dialysis.

The drug does cause thirst, polyuria (averaging over a gallon per day) and urinary frequency. It is not tolerated by all who take it, with about 10% to 16% of patients withdrawing from therapy in the REPRISE and TEMPO studies. Furthermore, persistent signals of elevated liver enzyme tests (fortunately with no cases of serious, irreversible liver injury in these trials, but at least one case of hepatic failure requiring liver transplantation attributed to tolvaptan) have led to the requirement of a risk evaluation and mitigation strategy (REMS) program with frequent and long-term monitoring of the liver.

Patients and their physicians will be very eager to learn more about tolvaptan in PKD and likely will wish to have the kidney function benefits, as they appear to be similar to those of renin-angiotensin-aldosterone system inhibitory therapy in diabetic nephropathy.

This journey from basic science through drug development and clinical trials has brought us an effective intervention in a disease for which we had nothing to offer for decades. However, the press release for the agent suggests an average wholesale drug cost of $13,041.10 per 28 days. While market pricing will likely be somewhat lower than this figure, the drug's cost and the cost for the REMS program will make it a very expensive proposition. In a prior cost effectiveness evaluation, Erickson and colleagues modeled an earlier start of tolvaptan that was estimated to delay ESRD by 6.5 years and result in enhancing average survival by 2.6 years (3). They utilized an estimated cost per month of tolvaptan of only $5760 and found that each extra quality adjusted life year would cost roughly $720,000 to $770,000. This poses quite the challenge.

Value-based healthcare is the most likely system that will succeed fee-for-service care. It calls for treatment decisions to be based on evidence—utilizing treatments that clearly benefit patients and improve the outcomes of overall healthcare. However, it also demands that healthcare dollars be used effectively, a call that most physicians would like to heed. At some point, this may mean bundled prices for both episodes of care and for disease management with the provider or provider group bearing responsibility for variation in costs.

As the costs for drug and device development are already extreme and rising, new innovations come with huge price tags and require careful consideration for value. Examples include novel cancer therapies, such as CAR-T (chimeric antigen receptor therapy) or improved antiviral therapies such as ledipasvir/sofosbuvir for hepatitis C; both have been considered great clinical advances but have raised questions about cost effectiveness. Healthcare economists have traditionally looked at cost effectiveness thresholds as prices that society should reasonably bear, and had fixed them at $50,000 per quality adjusted life year. However, many diseases (including ESRD care with dialysis) have required higher management costs and have pushed that threshold up toward $100,000 to $150,000 per quality adjusted life year (4). Others argue that you need to blend interventions, accounting for a mix of low-cost interventions and allowing some very high-cost interventions.

Still, for tolvaptan, some accommodation and planning will be needed. The FDA approval already limits the target population as those at "high" risk for progression. Per the Otsuka press release and general knowledge, risk factors for rapid disease progression include a substantially greater total kidney volume than expected for age, family history of end stage renal disease before 58 years of age, high blood pressure before 35 years of age, certain urologic events before 35 years of age (bleeding, pain, etc.), a historical decline in eGFR of ≥5 mL/min/1.73 m^2 within 1 year, certain inherited genetic profiles, and male gender.

Exactly what criteria will be considered per label by the FDA, and acceptable to payers in the United States, is yet to be seen. In other parts of the world, the approach has varied. In Europe, debates about utilizing risk scores such as the Mayo Clinic classification or the PRO-PKD score have led to differing approaches (5), potentially requiring single or multiple measures of total kidney volume; single or multiple measures of eGFR to define progression risk; as well as examination of family history, genetic findings, and symptoms or signs of disease. Similar approaches are sure to arise in the United States as we attempt to identify the patients most likely to benefit from tolvaptan. This may refine our choices to patients who are better able to benefit and in whom the cost may be more reasonable, but may independently add other costs (measuring the kidney, gene testing, more clinical decision time, prior authorizations, etc.)

Further studies must delineate the long-term benefits and risks, and study other populations, such as early disease, very late disease (to preserve GFR toward the end or even residual function in dialysis) in order to better define options for the most effective, highest value use of tolvaptan in PKD. Of course, the search for other therapies will continue, but for now, using what we have most effectively will be a key challenge and an important learning opportunity.

FDA approval for tolvaptan is a game changer; we must learn how to utilize it to the benefit of our patients and society. If we are fortunate, we will see other breakthrough therapies for our patients with kidney diseases. The hope is that this experience will allow us to gain wisdom regarding how to use them appropriately.

As the costs for drug and device development are already extreme and rising, new innovations come with huge price tags and require careful onsideration for value.

Richard Lafayette, MD, is Editor-in-Chief of Kidney News. *He is an investigator in the Otsuka PKD program and has received consulting fees in the past year.*

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Industry Spotlight

FDA approves First Anemia Biosimilar for Kidney Patients

The U.S. Food and Drug Administration recently approved Pfizer's biosimilar anemia drug, Retacrit (epoetin alfa-epbx). After two previous approval attempts, Retacrit was approved as a biosimilar to Epogen (Amgen) and Procrit (epoetin alfa, Johnson & Johnson).

Nephrologists as a group appear to be receptive to biosimilars for their patients. Spherix Global Insights reported their approval in a March 2018 survey of 202 nephrologists, especially if Retacrit use should become required by dialysis organizations. Only 22% of nephrologists surveyed agreed with the statement "I would not be pleased if my dialysis center switched to a biosimilar ESA."

The biosimilar will be offered later this year at a "significant discount" compared with the current wholesale acquisition cost of the reference product, Epogen, reported BioPharma.

Gaining approval as a biosimilar drug means the biosimilar can be prescribed for anemia in chronic kidney disease (and some other indications).

To receive the biosimilar instead of the reference product, a patient may need a prescription from a healthcare prescriber written specifically for that biosimilar.

In the fall of 2017, the FDA approved the first biosimilar drug indicated for renal cancer. Mvasi (bevacizumab-awwb, Amgen) was approved as a biosimilar to Avastin (bevacizumab, Genentech), according to HealthDay News.

Baxter's Data on Expanded Hemodialysis

Baxter International, in Deerfield, IL, has released data from two independent studies that explored expanded hemodialysis therapy (HDx) with its Theranova™ dialyzer. Expanded hemodialysis refers to applying high retention-onset membranes able to filter out molecules in the mid- to high molecular weight range.

Nephros (South Orange, NJ) gained FDA approval in 2012 for its hemodiafiltration system, the first in the US. Whereas dialysis works on a diffusion principle and filters smaller molecules, hemodiafiltration provides an extra boost of cleansing because it moves molecules through a fluid under pressure and forces out the large waste molecules that might otherwise remain.

The data compared outcomes of the Baxter dialyzer's ability to perform HDx versus outcomes with hemodiafiltration and were presented at the 55th Congress of the European Renal Association and European Dialysis and Transplant Association meeting in June. In both studies, HDx with the Baxter dialyzer was equivalent to the results of hemodiafiltration.

Baxter is hoping for FDA approval and announced a multicenter, prospective, randomized controlled clinical trial to support data submission for FDA marketing authorization. The system is already available in other parts of the world, including parts of Europe and Latin America, as well as Australia and New Zealand.

Positive Results for CKD Compound

Tricida, a privately held company based in South San Francisco, announced positive results from its most recent trial, a Phase 3 study of TCRA-301 to examine the drug's effects on metabolic acidosis in patients with chronic kidney disease (CKD). Tricida also filed for $150 million in an initial public offering to fund kidney drug approval.

Tricida's new compound TRC101, a novel, non-absorbed polymer, is designed to bind hydrochloric acid in the gastrointestinal tract and remove it from the body through fecal excretion, thereby decreasing the total amount of acid in the body and increasing blood bicarbonate.

The TRCA-301 trial met its primary and secondary endpoints in a statistically significant manner ($p < 0.0001$ for all primary and secondary endpoints) when compared with placebo, based on the initial analyses.

After 12 weeks, 59.2% of subjects in the TRC101 treatment group exhibited an increase in blood bicarbonate level of at least 4 mEq/L or achieved a blood bicarbonate level in the normal range of 22 to 29 mEq/L, compared with 22.5% of subjects in the placebo group.

For the secondary endpoint, the mean change in blood bicarbonate from baseline to week 12, subjects in the TRC101 treatment group exhibited a mean increase in blood bicarbonate of 4.49 mEq/L, compared with 1.66 mEq/L in the placebo group ($p < 0.0001$).

The overall safety profile of TRC101 observed in the trial was consistent with that expected for the general population of patients with stage 3 to 5 CKD and with similar non-absorbed polymer drugs with a site of action in the gastrointestinal tract, the company reported.

RenalGuard's New Heart Failure Trial Results

RenalGuard Solutions has announced results for an additional patient population with a form of heart failure. The Milford, MA, company demonstrated the ability of RenalGuard-Guided Diuretic Therapy to control and optimize fluid management in patients with acute decompensated heart failure. Heart failure is common in patients with CKD and end stage renal failure.

RenalGuard measures urine output and automatically infuses saline (hydration fluid) according to the ideal present fluid loss limits set by the physician.

Patients in the trial started with an initial 24 hours of standard treatment with furosemide (brand name Lasix, a loop diuretic), followed by 24 hours using the RenalGuard system.

The device alleviated symptoms related to heart failure, improving breathing patterns and increasing urine output. The device was designed to measure a patient's urine output and to respond by infusing hydration fluid based on the urine output level.

The company noted that during the RenalGuard cycle, patients developed more than a 2.5-fold increase in the amount of urine they produced. With furosemide, urine output averaged 1961 mL in 24 hours. With RenalGuard, urine output increased to an average of 4771 mL in 24 hours.

By day 30 after the trial, patients showed an average increase in the glomerular filtration rate of 8%. Three patients showed an increase of more than 25%.

In January 2018, RenalGuard announced positive results in patients with congestive heart failure. In that study, 10 patients used RenalGuard to manage fluids during diuretic therapy. It was the first-in-humans feasibility study focusing on a novel use of the RenalGuard System to manage fluids during diuretic therapy in congestive heart failure patients suffering from fluid overload.

A number of studies had already demonstrated RenalGuard's ability to protect patients from acute kidney injury following catheterization procedures when compared to the standard of care, including the MYTHOS trial, which found use of RenalGuard was superior to overnight hydration and the REMEDIAL II trial, which found RenalGuard was superior to sodium bicarbonate hydration.

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