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Clinician Update

Pulmonary Arterial Hypertension

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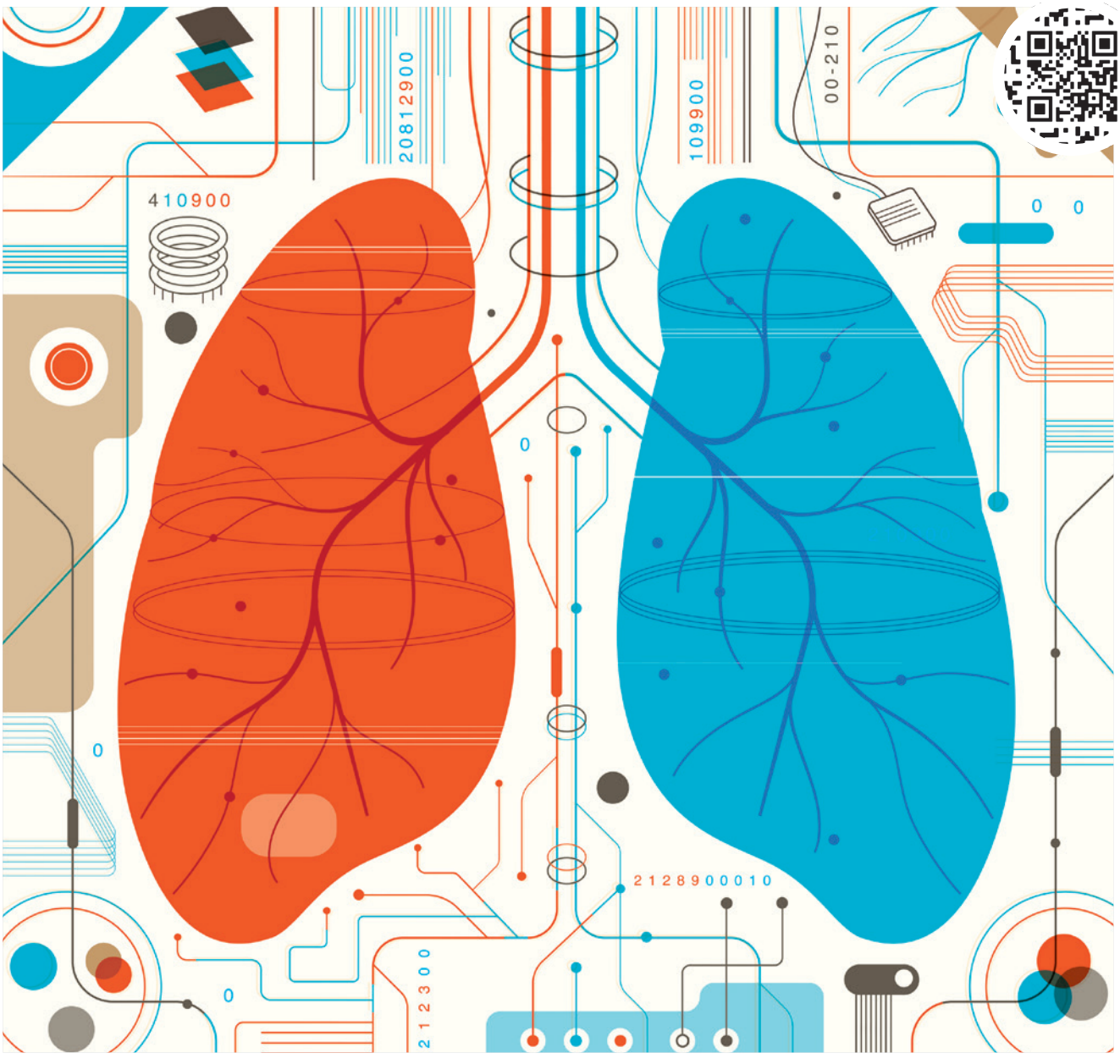

MODEL OF CARE

Insight on treatment options for PAH

BY ALEX EVANS, PHARMD, MBA

PAH can be challenging to manage, especially as the disease progresses and standard therapies are not enough to control the worsening symptoms. Here, experts shed light on options for escalating therapy to improve outcomes.

CONTINUED ON P. 4

Illustration by Harry Campbell

Pulmonary arterial hypertension (PAH) affects up to 1% of the global population and up to 10% of people over age 65.[1] A variety of treatment options are available to manage patients with PAH that have helped to delay mortality and improve quality of life for many patients. However, while survival outcomes with PAH are better than other forms of pulmonary hypertension (e.g., due to underlying cardiovascular or pulmonary disease), many patients still experience a heavy symptom burden and reduced longevity.Even with optimal treatment, it remains a progressive cardiopulmonary disease that often leads to death within several years of diagnosis.[2,3] Now, with the recent FDA approval of a novel treatment option, a targeted therapy is restoring hope to patients and the medical community alike.

The agent is a first in a new class of drugs called activin signaling inhibitors, which helps prevent the pulmonary vascular remodeling that is characteristic of pulmonary hypertension.[4,5] When used alongside background therapy, the agent has demonstrated promising results in increasing exercise capacity, improving lung function, prolonging the time to clinically worsening disease and extending life for patients living with PAH.[5]

"PAH is a disease that impacts a variety of homeostatic processes of the lung circulation. It's usually multiple things being dysfunctional and contributing to the disease," says Panagis Galiatsatos, MD, MHS, Associate Professor, Division of Pulmonary and Critical Care Medicine, and Director of the Tobacco Treatment Clinic at Johns Hopkins Medicine. "What I'm excited about with this medication is that it adds a different disease-targeting approach to PAH." (For more on this agent, see p. 6.)

Considerations for optimizing treatment

If treatment escalation is needed, a variety of therapeutic options are available for both disease-directed and supportive care.

In PAH, supportive care often consists of the use of diuretics to relieve edema as well as oxygen support. Oxygen therapy should be individualized based on patients' needs, with varying levels potentially needed for periods of exercise or sleep relative to those needed at waking rest.

Dr. Galiatsatos also advocates for the use of preventative vaccines as supportive care for patients with PAH. "A

> **"What I'm excited about with this medication is that it adds a different disease-targeting approach to PAH."**
>
> —PANAGIS GALIATSATOS, MD, MHS

Illustration by Matt Chinworth

lot of diseases [like PAH] rock patients' ability to have a physiological reserve to combat a second hit" he explains. As their lungs are battling PAH, if they get the flu or COVID, it'll do them in."

Some patients may also benefit from pulmonary rehab, which can help strengthen the muscles of the lungs using a tailored exercise program in a carefully monitored environment. "The goal is to maintain someone's strength through the disease," Dr. Galiatsatos explains. "The lungs are the gatekeeper to your endurance overall, so you want to maintain that as much as you can."

For patients with moderate-to-severe disease or risk, additional, disease-directed therapies should be initiated alongside supportive care. A right heart catheterization can help to assess vasoactivity and inform treatment decision making. Calcium channel blockers are often used first. Once blood vessels are no longer responsive to calcium channel blockers, other therapies should be considered. In many cases, these advanced therapies—phosphodiesterase-5 (PDE5) inhibitors and endothelin receptor agonists—are used together in a combination therapy approach. In fact, the FDA recently approved the first oral treatment that combines an endothelin receptor antagonist and a PDE5 inhibitor in a single pill.[5] Yet there is still more to be done, says Dr. Galiatsatos. "These medications are good, but for many patients, this is not a disease that they're going to overcome."

A novel mechanism of action that targets the root of the problem

The recent approval of the first activin signaling inhibitor marks a significant advance in the treatment of PAH, considering the complexity of the disease process. Pulmonary hypertension is a diverse group of conditions characterized by elevated pulmonary arterial pressure that increases the load on the right ventricle, causing symptoms like shortness of breath, especially with exercise, fatigue, hemoptysis and heart palpitation.[3] Eventually, this leads to right heart strain and failure.[6] Pulmonary hypertension is stratified into five groups, with Group 1 being PAH. The disease is characterized by pathological pulmonary vascular remodeling, which leads to narrowing and stiffening of the arteries and increased vascular resistance.[7]

It's long been known that the dysregulation of proliferative and antiproliferative signaling pathways are central to this vascular remodeling. A recently approved therapy targets this pathway by binding to and sequestering specific ligands in the transforming growth factor-beta superfamily, such as growth differentiation factor 11 (GDF11) and activin A. In preventing the downstream signaling cascades mediated by these ligands, an activin signaling inhibitor mitigates vascular remodeling, improves right ventricular function and slows progression of the disease.[8]

> "PAH is a severe form of heart and lung disease that leads to heart failure and a shortened life span. So there was a clear need to extend beyond [the current drug] pathways."
>
> —BRADLEY MARON, MD, FAHA

Bradley Maron, MD, FAHA, Director of the Pulmonary Hypertension Center at the University of Maryland Medical Center, describes the significance of this novel treatment option. "PAH is a severe form of heart and lung disease that leads to heart failure and a shortened life span. Before this approval, we had 14 drugs on the market, but they all targeted just three pathways: the nitric oxide pathway, the endothelin pathway and the prostacyclin pathway," says Dr. Maron. "So there was a clear need to extend beyond these pathways. [This approval] is a great example of how bench scientists can inform the medical community of promising new therapeutic targets that lead to improved outcomes for patients." Dr. Maron sees the agent's clinical trial data as very promising, explaining it had "a successful phase III trial that improved the 6-minute walk distance and nearly every secondary outcome across multiple domains, including quality of life, laboratory measures and functional status. The clinical trial was performed well and the effect sizes were also encouraging."

Implications for clinical practice

First, the foundation of any management plan for PAH is supportive care, notes Dr. Galiatsatos. This often consists of using diuretics to relieve edema, oxygen support and pulmonary rehabilitation for appropriate patients who are stable (see p. 16).

For patients with moderate-to-severe PAH, says Dr. Galiatsatos, disease-directed therapies should be initiated alongside supportive care. This may include calcium channel blockers, phosphodiesterase-5 inhibitors or endothelin receptor agonists. In many cases, these medications are used in combination therapy.[9,10] When PAH worsens and patients stop responding to their current therapy, an activin signaling inhibitor is an option for adjunctive use. And of course, when starting any medication, it's important to let patients know what to expect, including potential side effects. "Patients should be told to contact their provider whenever there are signs or symptoms of a possible adverse event," Dr. Maron stresses.

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Illustration by James Steinberg

PRACTICE PEARLS

Evidence-based guidelines for smoking cessation

For many patients who use tobacco, combining cessation agents with counseling is the key to quitting. These expert guidelines can help you implement a treatment plan tailored to their needs.

Recent data from a U.S.-based registry showed that nearly 62% of men and 43% of women with pulmonary arterial hypertension (PAH) have a history of smoking—along with a higher risk of earlier hospitalization and shorter survival after diagnosis, particularly in men. Why the risk was higher in men is unknown; however, one thing is certain: Any patient who continues to smoke after a PAH diagnosis is more likely to have exacerbated symptoms and poorer quality of life.[1,2]

Still, some patients are not being offered the help they need to quit. Case in point: Only 1 in 3 smokers received smoking cessation assistance during a cardiology visit, according to research by the American Heart Association. While the reasons are unclear, a lack of time during visits and the assumption that the primary care provider should discuss smoking cessation may be factors.[3,4]

Panagis Galiatsatos, MD, MHS, Director of the Tobacco Treatment Clinic and Associate Professor of Medicine at Johns Hopkins, can understand why physicians may not broach the topic, explaining, "If patients are still smoking in 2024 and they're an adult, you've got to think of them as the most refractory case." That can feel daunting for a clinician to attempt to take on. ►

But healthcare providers can have a positive impact on their patients' ability to quit. Here are counseling strategies that work.

Be anti-smok*ing*, not anti-smok*er*

Using a nonjudgmental tone is important for helping patients to open up. Reminds Dr. Galiatsatos, "This is a population that's been stigmatized and shamed." How he suggests thinking of it: "Tobacco is a legal product that has been placed in society and is used oftentimes in the most disadvantaged neighborhoods. Don't fault the person for what society has been allowing for hundreds of years," he says. Instead, look at smoking as requiring treatment, "like any other disease deserves," advises Dr. Galiatsatos.

Advise mindfulness

Dr. Galiatsatos encourages mindfulness when counseling a patient who smokes, having them question the reason they're doing it at the time (e.g., always after a meal or when stressed). Understanding why they reach for tobacco can help them get to the root cause. "That's key because they'll be living the same life as they did before—but without cigarettes as a coping mechanism," he explains. The more they call on mindfulness, he says, "the more they can deliberately pull away from the subconscious act of smoking. Ultimately, the goal is no longer simply to quit, but to learn to *stay* quit." Each time they're able to delay or say no to a cigarette, the stronger their ability to abstain in other situations.

Offer pharmacotherapy

When combined with counseling, medication can increase quit rates, but many patients are not offered this option. To assist clinicians, a multidisciplinary panel of experts, including Dr. Galiatsatos, coauthored the American Thoracic Society's clinical guideline on initiating pharmacotherapy in tobacco-dependent adults.[5] "These are guidelines, not rules," stresses Dr. Galiatsatos. "You should make the best decision for each patient." General recommendations:

Treat beyond 12 weeks.

The guideline panel concluded that extending the duration past the typical 12-week period used in clinical trials resulted in better outcomes with similar rates of adverse events as the shorter timeline.[6-9] While studies are usually done on a 12-week basis, that time period is often chosen because "that's how long the research grants lasted," says Dr. Galiatsatos, adding that a realistic timeframe for achieving the goal is longer, as with many medical treatments. "You wouldn't start a patient on a blood pressure medicine and say, 'You've got 3 months to reach blood pressure goals.' " Instead, extend treatment as necessary, provided the patient isn't having side effects. Even with the help of medication, "I've had patients take a total of 2 years to ultimately stop," Dr. Galiatsatos says.

Favor use of varenicline.

The guideline panel strongly recommends varenicline in multiple instances based on analysis of published research. Factors to keep in mind:

- ***It's more effective than bupropion and the nicotine patch.*** When analyzing varenicline and the nicotine patch head-to-head, the panel concluded that varenicline is preferred because it leads to longer periods of abstinence and may be better at reducing the risk of relapse.[10,11]

Varenicline is also recommended over bupropion, even though both work on the same neurotransmitter. While they each target dopamine to blunt the rewarding effects of smoking, varenicline goes one step further to block the nicotine receptors, says Dr. Galiatsatos. Some patients report feeling nauseated when they smoke while taking it because, he says, "the nicotine has to find other places to go." It's this extra step that makes it the more effective choice in achieving smoking abstinence and is recommended by the panel, despite its generally higher cost.

The expert panel also made two additional recommendations for varenicline labeled as "conditional," meaning there was not enough clinical data to garner a unanimous "strong" recommendation:

1) Varenicline may be used rather than electronic cigarettes. Although the panel was united in varenicline being the preferred intervention, the recommendation was left in question because the panel could not find any studies directly comparing the two.

2) Varenicline may be used in combination with a nicotine patch rather than using varenicline alone. However, there is some evidence that combining them may increase the risk of side effects such as insomnia, abnormal dreams and headache, so use caution when doing so.[12,13]

- ***It can be used in patients who have a psychiatric condition.*** Because of early black-box warnings—which have since been removed—varenicline has had limited use in patients with psychiatric disorders. But experts say it's time to reconsider the agent's role in this patient population. After reviewing two large randomized controlled trials that compared varenicline with a nicotine patch among participants with mental illness,[14,15] the panel concluded that varenicline was associated with a higher likelihood of cessation at 6 months without evidence of an increase in serious adverse events.

This is important, as smoking is particularly common among people with mental health disorders. According to the National Institute on Drug Abuse, some estimates put the prevalence of smoking among people with schizophrenia as high as 70% to 85% and for those with bipolar disorder at 50% to 70%.[16] With smoking as the leading cause of preventable death in all people, having varenicline as an option can be a game-changer for patients with psychiatric conditions, says Dr. Galiatsatos: "Working on these guidelines, we had a psychologist who stood up and said, 'This is going to save my patients' lives.' "

- ***It can work as a form of "pretreatment."*** The panel suggests using varenicline as a pretreatment—that is, prescribing it before a patient has indicated readiness to quit—

> "I tell the patient, 'I'm not asking you to become a nonsmoker overnight. Just start the medication and come back in 4 weeks.' "
>
> —PANAGIS GALIATSATOS, MD, MHS

Illustration by James Steinberg

because even those who are reluctant have higher success rates while taking it.[17,18] If you wait until the patient tells you they're ready to quit, Dr. Galiatsatos says, "You're delaying medical care for the patient."

Of course, pharmacotherapy should be presented as an option in a collaborative manner. "I tell the patient, 'I'm not asking you to become a nonsmoker overnight. Just start the medication and come back in 4 weeks,' " he says. After seeing how the medication can help curb their desire to smoke, they may be more willing to make the lifestyle changes that can support cessation.

If a patient isn't ready to start medication, Dr. Galiatsatos says to respect that decision—but let them know you'll be following up at the next visit to see if they've become more open to the idea.

Explain how medication helps—and why it's only part of the treatment plan.

While smoking-cessation agents are a crucial piece of the puzzle, they should always be combined with behavioral interventions. The analogy that Dr. Galiatsatos gives: "Say you wanted to run but your knees hurt, so you stop after taking a few steps." He likens these medications to taking a pain reliever to help you push through the initial discomfort. "They simply lower cravings so you can say no over and over again." In the meantime, he says, the patient has to do the work of learning new ways of coping. He tells them that by building new habits, "you're building a new identity as a nonsmoker." ●

–by Beth Shapouri

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Brief Summary of the Prescribing Information for WINREVAIR™ (sotatercept-csrk) for injection 45 mg, 60 mg, for subcutaneous use

DOSAGE AND ADMINISTRATION

Recommended Starting Dosage

WINREVAIR is administered once every 3 weeks by subcutaneous injection according to patient body weight. The starting dose of WINREVAIR is 0.3 mg/kg.

Obtain hemoglobin (Hgb) and platelet count prior to the first dose of WINREVAIR. Do not initiate treatment if platelet count is <50,000/mm^3 (<50 x 10^9/L).

Injection volume for starting dose is calculated based on patient weight as follows:

$$\textit{Injection Volume (mL)} = \frac{\textit{Weight (kg)} \times 0.3\ \textit{mg/kg}}{50\ \textit{mg/mL}}$$

Injection volume should be rounded to the nearest 0.1 mL.

For example: (70 kg x 0.3 mg/kg) ÷ 50 mg/mL = 0.42 mL, rounds to 0.4 mL

See Table 1 for selecting the appropriate kit based on calculated injection volume for starting dose.

Table 1: Kit Type Based on Injection Volume for Dose of 0.3 mg/kg

Injection Volume (mL)	Kit Type
0.2 to 0.9	45 mg kit (containing 1 x 45 mg vial)
1 to 1.1	60 mg kit (containing 1 x 60 mg vial)

Recommended Target Dosage

After verifying acceptable Hgb and platelet count, increase to the target dose of 0.7 mg/kg. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are required.

Injection volume for target dose is calculated based on patient weight as follows:

$$\textit{Injection Volume (mL)} = \frac{\textit{Weight (kg)} \times 0.7\ \textit{mg/kg}}{50\ \textit{mg/mL}}$$

Injection volume should be rounded to the nearest 0.1 mL.

For example: (70 kg x 0.7 mg/kg) ÷ 50 mg/mL = 0.98 mL, rounds to 1 mL

See Table 2 for selecting the appropriate kit based on calculated injection volume for target dose.

Table 2: Kit Type Based on Injection Volume for Dose of 0.7 mg/kg

Injection Volume (mL)	Kit Type
0.4 to 0.9	45 mg kit (containing 1 x 45 mg vial)
1 to 1.2	60 mg kit (containing 1 x 60 mg vial)
1.3 to 1.8	90 mg kit (containing 2 x 45 mg vials)
1.9 to 2.4	120 mg kit (containing 2 x 60 mg vials)

Missed Dose, Overdose, and Underdose

If a dose of WINREVAIR is missed, administer as soon as possible. If the missed dose of WINREVAIR is not administered within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals. In case of an overdose, monitor for erythrocytosis.

Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease

Check Hgb and platelet count before each dose for the first 5 doses, or longer if values are unstable. Thereafter, monitor Hgb and platelet count periodically.

Delay treatment for at least 3 weeks if any of the following occur:

- Hgb increases >2.0 g/dL from the previous dose and is above ULN.
- Hgb increases >4.0 g/dL from baseline.
- Hgb increases >2.0 g/dL above ULN.
- Platelet count decreases to <50,000/mm^3 (<50 x 10^9/L).

Recheck Hgb and platelet count before reinitiating treatment. For treatment delays lasting >9 weeks, restart treatment at 0.3 mg/kg, and escalate to 0.7 mg/kg after verifying acceptable Hgb and platelet count.

Preparation and Administration

Administration is subject to monitoring of hemoglobin and platelet count.

WINREVAIR is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer WINREVAIR when considered appropriate and when they receive training and follow-up from the healthcare provider (HCP) on how to reconstitute, prepare, measure, and inject WINREVAIR.

Confirm at subsequent visits that the patient and/or caregiver can correctly prepare and administer WINREVAIR, particularly if the dose changes or the patient requires a different kit.

Refer to the Instructions for Use (IFU) for detailed instructions on the proper preparation and administration of WINREVAIR.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Erythrocytosis

WINREVAIR may increase hemoglobin. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. In clinical studies, moderate elevations in Hgb (>2 g/dL above ULN) occurred in 15% of patients taking WINREVAIR while no elevations ≥4 g/dL above ULN were observed. Monitor Hgb before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter, to determine if dose adjustments are required.

Severe Thrombocytopenia

WINREVAIR may decrease platelet count. Severe thrombocytopenia may increase the risk of bleeding. In clinical studies, severe thrombocytopenia (platelet count <50,000/mm^3 [<50 x 10^9/L]) occurred in 3% of patients taking WINREVAIR. Thrombocytopenia occurred more frequently in patients also receiving prostacyclin infusion.

Do not initiate treatment if platelet count is <50,000/mm^3.

Monitor platelets before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine whether dose adjustments are required.

Serious Bleeding

In clinical studies, serious bleeding (e.g., gastrointestinal, intracranial hemorrhage) was reported in 4% of patients taking WINREVAIR and 1% of patients taking placebo. Patients with serious bleeding were more likely to be on prostacyclin background therapy and/or antithrombotic agents, or have low platelet counts. Advise patients about signs and symptoms of blood loss. Evaluate and treat bleeding accordingly. Do not administer WINREVAIR if the patient is experiencing serious bleeding.

Embryo-Fetal Toxicity

Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of WINREVAIR to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes, including increased embryo-fetal mortality, alterations to growth, and structural variations at exposures 4-fold and 0.6-fold (based on area under the curve [AUC]) those occurring at the maximum recommended human dose (MRHD), respectively. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with WINREVAIR and for at least 4 months after the final dose.

Impaired Fertility

Based on findings in animals, WINREVAIR may impair female and male fertility. Advise patients on the potential effects on fertility.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Erythrocytosis
- Severe Thrombocytopenia
- Serious Bleeding
- Embryo-Fetal Toxicity
- Impaired Fertility

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following data reflect exposure to WINREVAIR in the STELLAR trial. Patients (n=323) were randomized in a 1:1 ratio to receive WINREVAIR or placebo in combination with background standard of care therapies. Patients received a starting dose of 0.3 mg/kg via SC injection and the dose was increased to the target dose of 0.7 mg/kg administered once every 3 weeks for 24 weeks. After completing the primary 24-week treatment phase, patients continued into a long-term double-blind (LTDB) treatment period, maintaining their randomized treatment assignment, until all patients completed the primary treatment period. The median duration of treatment was 273 days in the placebo group and 313 days in the WINREVAIR group.

The most common adverse reactions occurring in STELLAR (≥10% for WINREVAIR and at least 5% more than placebo) are shown in Table 3.

Table 3: Adverse Reactions ≥10% in Patients Receiving WINREVAIR and at least 5% More Than Placebo in STELLAR*

Adverse reaction	Placebo N=160	WINREVAIR N=163
Headache	28 (17.5)	40 (24.5)
Epistaxis	3 (1.9)	36 (22.1)
Rash	13 (8.1)	33 (20.2)
Telangiectasia	7 (4.4)	27 (16.6)
Diarrhea	16 (10.0)	25 (15.3)
Dizziness	10 (6.2)	24 (14.7)
Erythema	5 (3.1)	22 (13.5)

*Double-blind placebo-controlled period + Long-term double-blind period of STELLAR

Increased Hemoglobin

Increases in Hgb were managed by dose delays (10%), dose reductions (6%), or both (5%). Shifts in Hgb from normal to above normal levels occurred in 87 (53%) patients receiving WINREVAIR and in 23 (14%) patients receiving placebo.

Thrombocytopenia

Decreases in platelets were managed by dose delays (2%), dose reductions (2%), or both (2%). Shifts in platelet count from normal to below normal occurred in 40 (25%) patients receiving WINREVAIR and in 26 (16%) patients receiving placebo.

Telangiectasia

In patients exposed to WINREVAIR who experienced telangiectasia, the median time to onset was 47.1 weeks.

Increased Blood Pressure

In patients taking WINREVAIR, mean systolic/diastolic blood pressure increased from baseline by 2.2/4.9 mmHg at 24 weeks. In patients taking placebo, the change from baseline in mean blood pressure was -1.6/-0.6 mmHg.

Treatment Discontinuation

The incidences of treatment discontinuations due to an adverse reaction were 4% in the WINREVAIR group and 7% in the placebo group. No specific adverse reactions causing treatment discontinuations occurred with a frequency greater than 1% and more often in the WINREVAIR group.

Uncontrolled Long-term Safety Data

The safety profile in the long-term uncontrolled extension period of the PULSAR study was generally similar to that observed in the STELLAR study. Patients were treated with WINREVAIR 0.3 mg/kg or 0.7 mg/kg (n=104) and had a mean duration of exposure of 151 weeks (maximum 218 weeks).

Continued on next page.

Brief Summary of the Prescribing Information for WINREVAIR™ (sotatercept-csrk) for injection 45 mg, 60 mg, for subcutaneous use (*continued*)

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. There are risks to the mother and the fetus associated with pulmonary arterial hypertension in pregnancy *(see Clinical Considerations)*. There are no available data on WINREVAIR use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies, administration of WINREVAIR to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including embryo-fetal mortality, alterations to growth, and structural variations at exposures 4-fold and 0.6-fold (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD), respectively *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is not known. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Report exposure during pregnancy or lactation to the Merck Sharp & Dohme, LLC Adverse Event reporting line at 1-877-888-4231.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In patients with pulmonary arterial hypertension, pregnancy is associated with an increased rate of maternal and fetal morbidity and mortality, including spontaneous abortion, intrauterine growth restriction, and premature labor.

Data

Animal Data

In embryo-fetal developmental toxicity studies, pregnant animals were dosed subcutaneously with sotatercept-csrk during the period of organogenesis. Sotatercept-csrk was administered to rats on gestation days 6 and 13 at doses of 5, 15, or 50 mg/kg and to rabbits on gestation days 7 and 14 at doses of 0.5, 1.5, or 5 mg/kg. Effects in both species included reductions in numbers of live fetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. In rats and rabbits, these effects were observed at exposures (based on area under the curve [AUC]) approximately 4-fold and 0.6-fold the maximum recommended human dose (MRHD), respectively. In rats only, skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae) occurred at an exposure 15-fold the human exposure at the MRHD.

In a prenatal and postnatal development study in rats, sotatercept-csrk was administered subcutaneously at doses of 1.5 and 5 mg/kg on gestation days 6 and 13, or at dosages of 1.5, 5, or 10 mg/kg during lactation on days 1, 8, and 15. There were no adverse effects in first filial generation (F1) pups from dams dosed during gestation at estimated exposures up to 2-fold the MRHD. In F1 pups from dams dosed during lactation, decreases in pup weight correlated with delays in sexual maturation at estimated exposures (based on AUC) ≥2-fold the MRHD.

Lactation

Risk Summary

There are no data on the presence of sotatercept-csrk in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with WINREVAIR, and for 4 months after the final dose.

Females and Males of Reproductive Potential

WINREVAIR may cause fetal harm when administered to pregnant women.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting WINREVAIR treatment.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with WINREVAIR and for at least 4 months after the final dose if treatment is discontinued.

Infertility

Based on findings in animals, sotatercept-csrk may impair female and male fertility. In male rats, although adverse histologic changes in reproductive organs were not reversible after a 13-week period, functional fertility demonstrated reversibility.

Pediatric Use

The safety and effectiveness of WINREVAIR have not been established in patients less than 18 years of age.

Geriatric Use

A total of 81 patients ≥65 years of age participated in clinical studies for PAH, of which 52 (16%) were treated with WINREVAIR. No differences in efficacy of WINREVAIR were observed between the <65-year-old and ≥65-year-old subgroups.

With the exception of bleeding events (a collective group of adverse events of clinical interest), there were no differences in safety between the <65-year-old and ≥65-year-old subgroups. Bleeding events occurred more commonly in the older WINREVAIR subgroup, but with no imbalance between age subgroups for any specific bleeding event.

Clinical studies of WINREVAIR did not include sufficient numbers of patients aged 75 and older to determine whether they respond differently from younger patients.

OVERDOSAGE

In healthy volunteers, WINREVAIR dosed at 1 mg/kg resulted in increases in Hgb associated with hypertension; both improved with phlebotomy. In the event of overdose, monitor closely for increases in Hgb and blood pressure, and provide supportive care as appropriate. WINREVAIR is not dialyzable.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information and IFU).

Discuss the following with patients prior to and during treatment with WINREVAIR.

Erythrocytosis

Caution patients that WINREVAIR may raise Hgb to levels that increase their risk of thrombotic events. Inform patients that Hgb levels will be assessed before at least the first 5 doses and then periodically, as dosage may need to be adjusted.

Severe Thrombocytopenia

Caution patients that WINREVAIR may cause platelet count to decrease, which if severe could cause bleeding. Inform patients that platelet count will be assessed before at least the first 5 doses and then periodically, as dosage may need to be adjusted.

Serious Bleeding

Inform patients of the possibility of serious bleeding, which is more likely to occur if they have low platelet counts or while on prostacyclin background therapy and/or antithrombotic agents. Advise patients to notify their healthcare provider about signs and symptoms of bleeding.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving WINREVAIR and for at least 4 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected during treatment with WINREVAIR. Report exposure during pregnancy or lactation to the Merck Sharp & Dohme, LLC Adverse Event reporting line at 1-877-888-4231.

Lactation

Advise females not to breastfeed during treatment with WINREVAIR and for 4 months after the final dose.

Females and Males of Reproductive Potential

Advise females and males of reproductive potential that WINREVAIR may impair fertility.

Administration by Patient or Caregiver

Review the IFU with the patient or caregiver step-by-step. Provide training to the patient or caregiver regarding proper preparation and administration of WINREVAIR and decide whether a patient or caregiver is capable of preparing and administering WINREVAIR independently.

Make sure the patient or caregiver can do the following correctly:

- reconstitute the medicine,
- measure the correct amount of medicine according to the patient's prescription,
- select and prepare a proper injection site, and
- inject the medicine subcutaneously.

Incorrect Dose or Missed Dose

Inform patients to call their healthcare provider for further instruction if they take more than or less than the correct dose. Advise them about signs/symptoms to monitor for and what to do if any of these signs/symptoms should occur. Advise them that additional laboratory tests may be required prior to the next scheduled dose to ensure that the next dose can be safely administered.

Instruct the patient that if they miss the prescribed dose of WINREVAIR, they should take it within 3 days and maintain the original schedule for the next dose. If not taken within 3 days, instruct them to call their healthcare provider for guidance.

For more detailed information, please read the Prescribing Information.

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MERCK

IMPROVING QUALITY OF LIFE WITH PULMONARY REHAB

Although PAH is a life-changing diagnosis, comprehensive intervention programs can help patients better manage their disease and improve their quality of life.

For patients with pulmonary arterial hypertension (PAH), pulmonary rehabilitation (PR) offers personalized education, exercise and behavioral change therapies in a medically supervised setting with a multidisciplinary team of healthcare providers. The European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines recommend that PR be considered under supervision in patients with PAH who are on optimal medical therapy and are clinically stable.[1] The latest research confirms the benefits of supervised PR for this patient group, including significant improvements in exercise capacity, physical strength and quality of life.[2] Additionally, studies have shown that after participation in PR, hospital admissions and length of hospital stays decreased significantly, including PAH.[3]

Continued on p. 18 ►

Illustration by Benjavisa / Getty Images

> "We personalize their education, so they can try new breathing techniques and figure out how to control their shortness of breath."
>
> —KATRINA A. ROUX-BERNSTEIN, CRNP

"Pulmonary rehabilitation is one of the best ways for patients to build strength and endurance," says Joel D. Provenzano, MD, pulmonologist at OhioHealth Marion General Hospital in Marion, OH. "The emotional and social benefits that PR provides make daily life easier and better for patients." Here, expert insight on what makes PR programs so invaluable—and why appropriate patients should be referred and encouraged to participate.

Team collaboration

"PR is a multidisciplinary effort," explains Katrina A. Roux-Bernstein, CRNP, a pulmonary nurse practitioner at the University of Maryland Baltimore Washington Medical Center, which is why programs typically include a pulmonologist, registered nurse, exercise physiologist and dietitian as well as respiratory, physical and occupational therapists.[3] The team works with patients in an outpatient setting or hospital rehabilitation center.

All programs require a referral from a physician, and they begin and end with an evaluation for comorbidities, smoking status and overall physical and psychological health, as well as monitoring patients as they walk at a normal pace for 6 minutes. The results of the evaluation and 6-minute walk test reveal the patient's functional exercise capacity and help clinicians establish individualized treatment.[2,3] "The evaluation lets us personalize a patient's PR program based on their current needs and future goals," says Dr. Provenzano. "We collaborate with the patient to create a plan that is feasible."

Personalized education

The education portion of PR includes assessments, classes and treatment plans for disease management, smoking cessation, nutrition, stress, breathing retraining and lifestyle habits.[2,3] "Our goal is to help patients learn how to better manage their PAH," says Roux-Bernstein. "We personalize their education, so they can try new breathing techniques and figure out how to control their shortness of breath," she says. "We also teach them how to recognize worsening symptoms and when to contact their healthcare provider or call 911."

Monitored (and motivating) activity

Physical inactivity is common among PAH patients who often have comorbidities that make exercising daunting. A supervised rehab exercise program involves endurance training, upper and lower extremity exercises as well as interval and resistance training. A healthcare provider will monitor the patient's blood pressure, heart rate, respiratory rate, oxygen saturation and overall response while they train.[1-3]

"Part of the rehabilitation is making the exercises more challenging over time," says Robert L. Schiffman, MD, pulmonologist at Mount Auburn Hospital in Cambridge, MA, and instructor at Harvard Medical School. "Their conditioning improves when we change the force and amount of work a patient has to do."

Another benefit of PR exercise training is that it reduces dyspnea, one of the most disabling symptoms of PAH. "Increasing muscle metabolism allows a patient to tolerate more exercise with less dyspnea," says Dr. Schiffman. "And this motivates them to stay active."

Increased confidence

PR boosts a patient's self-assurance and ability to engage in more activities, so daily tasks become easier.[2,3] "Patients gain confidence during PR because they can do more activities like going to the grocery store," Dr. Schiffman says, adding, "They feel more independent, which improves their quality of life."

PR can also desensitize patients to dyspnea, which helps allay their fears. "When patients experience shortness of breath, they want to stop exercising," Dr. Provenzano notes. To combat this, Roux-Bernstein explains, "If a patient is hyperventilating and anxious, we can show that their vitals are okay and that it's safe for them to continue."

Reduced hospital readmissions

According to the PAH guidelines and a report from the American Thoracic Society, a review of randomized controlled trials revealed fewer readmissions for patients who started PR during hospitalization or within 4 weeks of being released from the hospital.[1,3] Doctors agree that they see fewer exacerbations and hospitalizations for those severe chronic respiratory diseases patients who participate in PR. For example, Dr. Provenzano notes that data from 2018, the last full year before the pandemic that shut down PR programs, showed a 3% hospital readmission rate for patients who had 36 sessions of PR versus 15% to 20% readmission rates for patients who did not do PR.

Stronger social bonds, less depression

Another benefit of PR, experts say, is the opportunity to socialize with other patients, which helps lower depression. "When PR programs closed during the pandemic, we saw a lot of patients struggle with depression," recalls Dr. Provenzano. "Since reopening, patients once again had a reason to go out. By building social connections and interacting with others in the program, they are less likely to have symptoms of depression."

Clinicians agree that the social support PR provides leads to greater self-esteem. "PAH can isolate patients at home, which limits their social interactions," says Roux-Bernstein. "Pulmonary rehab gives patients the opportunity to exercise with their peers and form new social bonds." Dr. Provenzano says he has seen many patients form friendships with other PR participants that last long after the program ends. "PR can provide social and emotional support that is missing in many patients' lives," he says.

—by Lana Bandoim

References

1. **Humbert M, et al. The European Society of Cardiology (ESC) and European Respiratory Society (ERS) issued revised PAH care recommendations: 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *Eur Respir J*. 2022;43(38):3618-3731.**
2. **Yan Lu, et al. The benefit of exercise-based rehabilitation programs in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials. *Pulm Circ*. 2021;11(2):1-8.**
3. **Holland AE, et al. Defining modern pulmonary rehabilitation. An official American Thoracic Society Workshop Report. *Ann Am Thorac Soc*. 2021;18:e12-e29.**

Figure 1.

Key components of pulmonary rehab[3]

1 Patient assessment
- An initial center-based assessment by a healthcare professional
- An exercise test at the time of assessment
- A field exercise test
- Quality-of-life measure
- Dyspnea assessment
- Nutritional status evaluation
- Occupational status evaluation

2 Program components
- Endurance training
- Resistance training

3 Quality assurance
- Healthcare professionals are trained to safely deliver the components of the model that is deployed

4 Method of delivery
- An exercise program that is individually prescribed
- An exercise program that is individually progressed
- Team includes a healthcare professional with experience in exercise prescription and progression

PATIENT: CLAIRE, 67, HAD A HISTORY OF HYPOTHYROIDISM AND HYPERLIPIDEMIA. SHE WAS DIAGNOSED WITH PULMONARY ARTERIAL HYPERTENSION IN 2014.

"A third therapy could make a huge difference"

PHYSICIAN:

Vallerie V. McLaughlin, MD

Professor of Cardiovascular Disease and Internal Medicine, Frankel Cardiovascular Center, University of Michigan Health, Ann Arbor

Treatment history:
When Claire first came to see me, she had symptoms of pulmonary arterial hypertension (PAH) that were indicative of WHO functional class (FC) III and a 6-minute walk distance (6MWD) of 395 meters. After a series of tests, including a right-heart catheterization, I started her on dual oral therapy that included an endothelin receptor agonist and a phosphodiesterase-5 inhibitor. Within a few months, she improved to FC II and was able to walk more than 500 meters. A repeat right-heart cath also showed improvement.

Claire did well for many years, but recently her dyspnea has progressed. Her most recent echocardiogram revealed mild-to-moderate right ventricular (RV) enlargement, mild RV dysfunction, moderate tricuspid valve regurgitation and an estimated RV systolic pressure of 80, plus an estimated right atrial pressure of 8 mmHg. Claire's 6MWD also declined by about 75 to 100 meters from her previous 6MWD—essentially putting her back to square one. While she usually enjoyed visits from her grandchildren, she found herself becoming increasingly out of breath when trying to keep up with them. Even mild exercise, like gardening, was becoming difficult. A repeat right-heart cath showed clinical worsening of her PAH.

Initiating treatment:
Claire was very eager to try an additional medication. We discussed several therapies, including prostacyclin pathway agents, which deserve consideration for patients who are no longer meeting the criteria for low-risk PAH on dual oral therapy. However, we also talked about a recently approved therapy, an activin signaling inhibitor therapy. This agent, a biologic that represents a new drug class for PAH, has shown improvements in 6MWD, hemodynamics and clinical worsening in PAH patients on standard background therapy. Claire and I reviewed the potential side effects, among them an increase in hemoglobin. Fortunately, her hemoglobin and platelets were normal, so she was a good candidate for the drug. We also discussed how this treatment would be administered, as well as the importance of doing a complete blood count to check her hemoglobin and platelets prior to each of the first several doses.

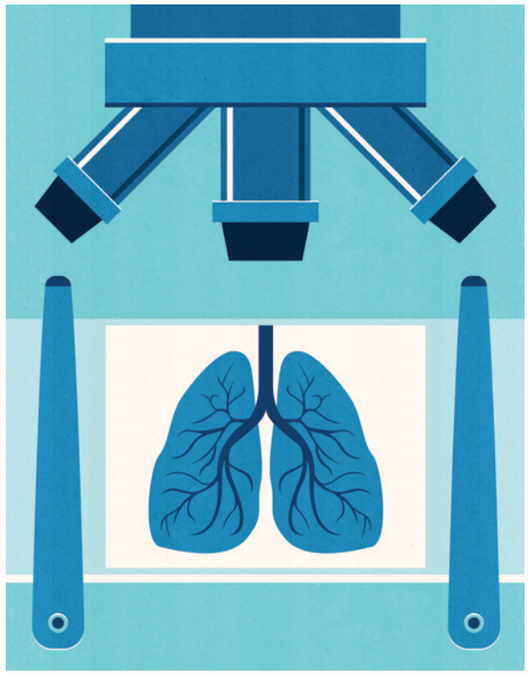
Considerations:
It's important to frequently reassess patients with PAH and determine their risk status. Those who don't meet low-risk criteria should immediately be considered for escalation of therapy. Thankfully, we have many good PAH therapies to offer. In Claire's case, she wasn't meeting her goals on dual oral therapy. However, she was an excellent candidate for a recently approved therapy, without any contraindications. In part, too, because of the drug's impressive clinical trial results, she opted for it as her third PAH therapy. It's too soon to tell how well Claire is doing on her new therapy (she just got her first dose last week), but combined with exercise, pulmonary rehab and a low-sodium diet, I'm expecting this third therapy for PAH to put her on a path to much better lung function.

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Claire's case.

Q

A

Managing pulmonary arterial hypertension (PAH)



DIFFERENTIAL DIAGNOSIS

Q: Certain comorbidities can mask symptoms of PAH. What can aid diagnosis?

A: Developing a sufficient working list of differential diagnoses is essential for medical providers to deliver safe and effective care. Often, patients present with other comorbidities that mask the underlying disease, making it difficult to discover a working diagnosis. PAH can be quite difficult to detect when a patient has multiple comorbidities. Patients often present with rapid onset of dyspnea at rest, severe hypoxemia, tachypnea and tachycardia. The first inclination for this patient is typically directed towards a differential diagnosis of asthma, pneumonia, COPD exacerbation, or even heart failure as these are common ailments often seen in an emergency setting. The physical exam is the most important part of discovering PAH in patients with severe hypoxemia. The most sensitive finding on an examination for PAH is a prominent second heart sound that is heard in 90% of idiopathic PAH patients. You will also be able to hear an audible wheeze and crackles as the alveolar flooding and compression of the airways proceed to restrict movement through the lungs. Through a series of tests such as PFTs, CXR, serology, ABGs, cardiac catheterization and echocardiogram, there should be enough information to determine if the cause is lung disease or heart disease. However, if one cannot determine the cause of the distress, a V/Q scan is often done to rule out pulmonary embolism or primary pulmonary hypertension. Studies show that in patients with systemic sclerosis who are asymptomatic, those who receive yearly cardiopulmonary screening tend to be diagnosed with PAH earlier than those who are not screened. This is often a condition diagnosed by exclusion.

*–**Jamie Latimer, MSN, AGACNP-BC,** cardiac and acute care clinician, UC Health of Colorado*

FLUID RETENTION

Q: What role do diuretics play in treating PAH?

A: Providers have some great options to offer their patients to ensure a better quality of life. These include diuretics, oxygen and inotropes (e.g., digoxin). Diuretics play an important role in PAH treatment by helping to diminish sodium reabsorption and therefore decrease fluid retention. This can alleviate PAH symptoms by decreasing the accumulation of fluid in the lungs, improving ventilation and ease of breathing. Diuretics are typically taken once a day at the beginning of treatment, but as the disease advances, escalated dosing and combinations of two diuretics are often used. Patients also need periodic monitoring to evaluate the loss of potassium and other electrolytes through urine elimination.

*–**Jamie Latimer, MSN, AGACNP-BC***

Illustration by Kotryna Zukauskaite

COPING SKILLS

Q: How can clinicians help patients cope with the psychosocial aspects of having PAH?

A: PAH can make everyday tasks and work hard to manage, causes significant stress and can lead to social isolation, seriously affecting a patient's overall quality of life. To help patients cope, it's crucial to establish a strong partnership with them. Be up front with patients about their prognosis and available treatments. Then create a management plan with shared decision-making–and really listen to their concerns and preferences. When patients feel heard and respected, they're more likely to trust their doctor and actively participate in their own care.

It's also important to take a multidisciplinary approach that includes PAH specialists who can offer patients personalized advice on nutrition, suitable exercises and resources to cope with the psychosocial impact of living with the disease. This holistic approach can enhance both their physical health and overall well-being, making sure they get comprehensive care tailored to their specific needs. To facilitate this, I refer patients to pulmonary rehab and encourage their participation in support groups such as those offered by the Pulmonary Hypertension Association (*phassociation.org*).

*–**Raj Dasgupta, MD,** Division of Pulmonary, Critical Care and Sleep Medicine, USC Keck School of Medicine; Chief Medical Advisor for* Sleep Advisor

SLEEP APNEA

Q: What is the connection between sleep apnea and PAH?

A: People who have obstructive sleep apnea (OSA) are at risk of developing PAH, and patients with both conditions have greater functional limitation than patients who have OSA alone. Those who suffer from both have an increased breathing workload because of the fluid accumulation in the lungs. This in turn increases the oxygen requirement, adding a significant stress on the heart. In addition, respiratory muscles become rapidly fatigued, placing the patient at risk for cessation of ventilation.

Research also shows that patients with elevated pulmonary pressures also have narrower airway closure during tidal breathing. This then causes ventilation perfusion mismatch, leading to increased tone in the pulmonary vasculature in response to hypoxia. Fortunately, studies have found that those who used CPAP nightly have a mean reduction in pulmonary artery systolic pressure of 15 mmHg compared with those who used diuretics and oxygen therapy alone. This underscores the need to identify patients who have either OSA or PAH and be vigilant for signs of the other condition. Patients with PAH have a high mortality rate if their OSA is left untreated.

*–**Jamie Latimer, MSN, AGACNP-BC***

> "It's crucial to establish a strong partnership. Be up front with patients about their prognosis and available treatments."
>
> —Raj Dasgupta, MD

SPECIAL THANKS TO OUR MEDICAL REVIEWER:

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Health Monitor

Clinician Update

EXAM TOOL

Assessing severity of PAH symptoms

When pulmonary arterial hypertension (PAH) progresses, the symptoms are often nonspecific and insidious, with two of the earliest signs being dyspnea and reduced ability to do routine activities. This underscores the importance of assessing not only objective measures, such as arterial pressure, but also subjective measures of how the patient is feeling day to day. When assessing worsening symptoms—which may require escalation of therapy—consider the following criteria.

DYSPNEA

ASK PATIENTS WHICH OF THE FOLLOWING BEST DESCRIBES THEM:

Mild

- ☐ I only get breathless with strenuous exercise.

Moderate

- ☐ I get short of breath when hurrying on level ground or walking up a slight hill.

Moderate-to-severe

- ☐ I walk slower than people of my same age because of breathlessness.
- ☐ I have to stop for breath when walking at my own pace on level ground.
- ☐ I can't do my usual exercise routine, or i don't do it as often, because I get breathless.

Severe

- ☐ I stop for breath after walking a few yards, or a few minutes, on level ground.
- ☐ I get breathless walking to or back from the mailbox.

Most severe

- ☐ I am too breathless to leave the house.
- ☐ I am breathless when dressing or undressing.

OTHER SYMPTOMS

ASK PATIENTS THE FOLLOWING:

If you have experienced any dizziness in the last few weeks, how would you describe it?

- ☐ Less severe than usual.
- ☐ About the same as usual.
- ☐ More severe than usual.

If you have experienced any swelling in your legs, feet and abdomen in the last few weeks, how would you describe it?

- ☐ Less severe than usual.
- ☐ About the same as usual.
- ☐ More severe than usual.

If you have been prescribed oxygen, how would you describe your oxygen use in the last few weeks?

- ☐ I use oxygen while sleeping at night.
- ☐ I use oxygen during physical activities.
- ☐ I use oxygen most of the day and night.
- ☐ I have not been using oxygen.

GENERAL ACTIVITIES

ASK PATIENTS THE FOLLOWING:

In the last few weeks, have you missed work or doing normal daily activities due to chest pain, fatigue, swelling or worsened shortness of breath?

- ☐ No
- ☐ Yes (please explain) _____
  _____
  _____

In the last few weeks, have you been able to do your routine activities at the same frequency as usual?

- ☐ I have increased the frequency of one or more activities.
- ☐ I am able to do all of the same activities at the same frequency.
- ☐ I have cut back on the frequency of one or more activities.
- ☐ I have completely stopped doing one or more activities.

Source: Didden EM, et al. *Pulm Circ.* 2023;13(1):e12188.
Illustration by kei_gokei / Getty Images