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IN THIS ISSUE

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Got the time? Pharmacists excel at adverse drug detection on chart review

But with time constraints auto systems more practical

When they have time to do the work, pharmacists perform better than non-pharmacists in manually reviewing charts to determine inpatient adverse drug events (ADEs). That's the conclusion of a systematic review and meta-analysis conducted by researchers at the University of Utah, Salt Lake Informatics, Decision Enhancement, and Surveillance Center, and Department of Veterans Affairs Medical Center in Salt Lake City.[1]

The research was conducted to determine if studies that included pharmacists as chart reviewers detected higher rates of adverse drug events than studies that included other healthcare professionals or hospital personnel as chart reviewers. Lead author **Shobha Phansklar**, MS, at the University of Utah Department of Biomedical Informatics, tells *Drug Formulary Review* the study did not address the cost-effectiveness of using pharmacists as chart reviewers and she conceded it may be difficult for them to find time for chart reviews. While pharmacists' training in therapeutics and comprehensive drug knowledge makes them an obvious choice for ADE surveillance, chart review is a resource-intensive process that takes pharmacists' time away from patient care activities. The allocation of pharmacists' time in chart review can be justified by determining whether pharmacists are capable of detecting a greater number of ADEs than other healthcare professionals such as nurses and physicians, or non-clinical personnel who are engaged in ADE surveillance.

Many clinical organizations have recognized the importance of establishing mechanisms for adverse drug event surveillance. Hospitals are mandated to have ongoing drug surveillance programs in place to detect and evaluate drugs' effects and to propagate safe, appropriate, and effective drug therapies. Phansklar says several surveillance methods are used in clinical settings to detect ADEs. Voluntary spontaneous reporting systems are commonly used, she says, but reporting has been said to be as low as 1.5%. Computer-assisted techniques are used in some hospitals, but they require sophisticated clinical information systems and often lack

the ability to search through progress notes for textual signals, thus not exploring a considerable amount of data. Manual chart review has resulted in high detection rates with the ability to identify a greater number of ADEs than other methods. That technique also offers the potential to extract implicit clinical information from free-text documents such as progress notes, nursing notes, and discharge summaries. "Manual chart review is therefore considered the gold standard in ADE detection," Phansklar says. "Despite these advantages, chart review requires relatively large resource use and expense, thus limiting its use to research studies."

Dearth of data

A total of 661 abstracts were identified in a literature search, and 46 studies potentially met the inclusion criteria. Some 13 studies meeting the inclusion criteria and including either pharmacists or non- pharmacists as chart reviewers were included in the final analysis. Meta-analysis of the 13 studies comparing chart reviews performed by pharmacists with those performed by other healthcare professionals or hospital personnel revealed that pharmacists detected higher ADEs per admission as compared with non-pharmacists. Phansklar cautions there is not much scientific literature reporting high-quality studies using chart review for detecting inpatient ADEs. Despite searching a broad range of databases, the researchers found only a small number of studies meeting all inclusion criteria. Most of the excluded studies looked at outpatient ADEs, medication-related admissions, or evaluation of ADEs related to specific drug classes or specific ADE types.

The researchers said they made every effort to determine the profession of the reviewers from the data reported in the studies. They recommended that future studies make an effort to describe in greater detail not just the clinical background of chart reviewers but also other relevant characteristics that can give rise to heterogeneity, such as the pieces of information reviewed in patients' medical records. Another factor identified as contributing to heterogeneity was the criteria used for assessment of ADE characteristics. "In our review we found a staggering number of disparate criteria used to assess various characteristics of an ADE," they reported. "The World Health Organization definition and its related terminology are used in many studies to determine the likelihood of an event being an adverse drug reaction, but standards for deriving conclusions about the causality, severity, and preventability are absent. The lack of such standards limits the validity of case identification across ADE studies." Phansklar says that despite overwhelming evidence of statistical heterogeneity, the numbers pertaining to ADE rates detected by the two groups were large enough to indicate significant differences. "However," she says, "it is difficult to state that actual differences exist in light of the heterogeneity that exists among the studies. Nevertheless, despite the heterogeneity, there is strong evidence that pharmacist-led interventions based on chart review report a higher ADE rate among inpatients. Our data suggest that pharmacists are the most thorough chart reviewers. Pharmacists' knowledge of drugs and clinical therapeutics may give them an advantage over other clinicians for the purpose of inpatient ADE

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detection. As awareness of patient safety issues increases, pharmacists find themselves more engaged in ADE surveillance activities. However, dedicating full-time clinical pharmacist positions to ADE chart review is expensive and difficult to justify, in part because of the expanded clinical role pharmacists play in the inpatient setting. Our data support allocation of clinical pharmacists' time for ADE surveillance studies that are aimed at detecting higher sensitivities of ADE frequency among inpatients. Owing to the disparity in the criteria used for ADE detection, we could not derive a conclusion about the specificity of attributing ADEs."

Automation may be a solution

The researchers suggest that chart review automation may provide a potential solution for making ADE surveillance less expensive and more efficient for pharmacists. To work, Phansklar tells *DFR*, such systems need to incorporate the cognitive reasoning used by pharmacists when conducting automated chart reviews. "It is important to note that in the studies that we reviewed," she says, "pharmacists were not limited to only medication orders or laboratory values, but also took into account any textual signals that existed in the medical record, such as progress notes, shift assessments, and pharmacist notes. This is significant for developing automated ADE surveillance systems to aid pharmacists in the chart-review process. Researchers should focus on capturing the pharmacists' cognitive framework, not just for being able to reason about the appropriateness of medications, but also for reasoning about additional textual signals that pharmacists routinely take into consideration when deliberating about an ADE."

Phansklar and colleagues are working on developing an automated chart review system and trying to identify the items that pharmacists find to be important when they review a chart. Focus groups are used to identify the triggers that pharmacists use. Phansklar has received a number of e-mails from people wanting to learn more about the study. "People want to see pharmacists involved in ADE studies," she concludes, "but need a scientific basis."

Reference

1. Phansklar S, Hoffman J, Nebeker J, et al. Pharmacists versus Nonpharmacists in Adverse Drug Event Detection: A Meta-analysis and Systematic Review, *Am Jrl Health-System Phar*. 2007;64(8):842-849. ■

Pharmacists cite personal reasons for refusing to fill

Personal autonomy vs societal duty

Increasingly, pharmacists are becoming involved in controversies over their right to refuse to fill a prescription. **Emily Evans**, PharmD, an assistant professor of pharmacy practice in the University of Louisiana at Monroe College of Pharmacy, says that although the issue has recently gained public attention because of situations involving emergency contraception such as Barr Laboratories' Plan B, in fact it is not a new issue to the pharmacy profession.

Writing in the *American Journal of Health-System Pharmacy,* Evans says many pharmacists also have strong feelings about dispensing drugs used for assisted suicide, euthanasia, and capital punishment, and have ethical questions regarding dispensing erectile dysfunction drugs for convicted sex offenders and HIV-positive patients.

"Delegates at a meeting of the American Medical Association have even claimed that pharmacists refused to fill prescriptions for psychotropic and pain medications because of moral objections," she says, "although no documented cases of pharmacists refusing to fill a legitimate prescription for these agents have been reported in the literature or news sites."

Many pharmacists believe that no one should question their right to refuse to dispense a prescription for religious, moral, or ethical reasons. They say this is a right supported by two basic societal principles: nonmalfeasance and professional autonomy. The principle of nonmalfeasance is cited by many who practice the right to refuse, according to Evans, because they believe that dispensing the requested drug can cause harm to another human being, whether it is a fetus, a prisoner on death row, a terminally ill patient, or a potential sex partner of an HIV-positive patient. Professional autonomy is cited even more frequently, as members of all professions are given an opportunity to decline to offer services for ethical reasons and pharmacists are asking for the same treatment as afforded physicians, lawyers, and clergy.

But not everyone agrees. Evans refers to one author's statement that, "When duty is a true duty, conscientious objection is wrong and immoral." Some would argue, she says, that if a

pharmacist is not prepared to offer legally permitted, efficient, and beneficial care to a patient because it conflicts with his or her values, then he or she has chosen the wrong profession. Those who do not support a pharmacist's right to refuse to fill a prescription say that those who invoke this "right" are denying patients medications for purposes deemed legitimate by their physicians, and it is their duty to dispense the drug. Also, they say, most outpatient pharmacists don't have access to patients' complete medical records and thus are not fully equipped to make clinical decisions that affect a patient's health because they do not, and cannot, know the entire situation.

Professional organization policies

The American Society of Health-System Pharmacists (ASHP) and other professional pharmacy organizations have developed policies on the topic and have shared them with legislators. ASHP recognizes a pharmacist's right to decline to participate in therapies that he or she finds morally, religiously, or ethically troubling, and supports establishment of systems protecting patients' right to obtain legally prescribed and medically indicated treatments while reasonably accommodating in a non-punitive manner a pharmacist's right of conscience.

Evans says the goal of ensuring patient access to legally prescribed, clinically appropriate therapy while allowing the pharmacist to step away from a situation because of personal beliefs is consistent among the policies of the American Pharmacists Association, American College of Clinical Pharmacy, and Academy of Managed Care Pharmacy. She says there also are organizations within the medical community whose policies mirror this underlying intent. Thus, the American Academy of Family Physicians believes that a pharmacist's right of conscientious objection should be reasonably accommodated, but that governmental policies must be in place to protect patients' rights to legally prescribed, medically indicated treatments in a timely manner.

As of May 2006, Evans reports, 10 states had enacted laws addressing the subject, with four of the states (Arkansas, Georgia, Mississippi, and South Dakota) allowing a pharmacist to refuse to dispense emergency contraception, and four (Colorado, Florida, Maine, and Tennessee) providing broad refusal clauses for healthcare professionals that do not specifically mention pharmacists or specific drugs. Illinois passed an emergency rule in 2005 requiring a pharmacist to dispense contraception subsequent to a legitimate prescription, and California pharmacists have a duty to dispense prescriptions and can refuse to dispense them only when their employer approves the refusal and the patient can still access the medication elsewhere in a timely manner.

At the time Evans wrote her analysis, there were 48 bills in legislatures in 21 additional states. Some 37 of the 48 bills would expressly give pharmacists and other healthcare providers the right to refuse to participate in activities that they find morally or ethically objectionable. Many of these bills would exempt the healthcare providers from legal consequences or disciplinary action from their employer or state board of pharmacy.

Bills take different approaches

Of the 37 proposed bills supporting the right to refuse, eight specifically mention emergency contraception; two deal with family planning issues, and seven deal with procedures of products resulting in abortion or termination of pregnancy. Of the 11 proposed bills that expressly prohibit the pharmacist's right to refuse, or impose fines on those who do, none mention specific drugs or procedures. Evans tells *Drug Formulary Review* that while many states are moving forward with legislation, there may ultimately need to be a national solution. It is imperative, Evans says, that new pharmacists be familiar with several aspects of the issue:

His or her views on controversial drugs and topics. Knowing the situations that are likely to present an ethical or moral problem ahead of time can help avoid potential problems in practice. Employers and coworkers should be made aware of any objections that are held. Pharmacists should try to determine how situations will be handled before they arise.

His or her employer's policies. As long as it does not violate state or federal law, employers have a right to set any policy that they choose regarding this issue. Ensuring employment with an entity that shares the pharmacist's viewpoint can help avoid conflict in future situations.

The laws and board of pharmacy rules in the pharmacist's state. Legislation on this dynamic issue is quickly changing. Regardless of a pharmacist or employer's viewpoints, state law will take precedence. Violating pharmacy board rules, whether actual legislation or not, can result in injunctions

against a practitioner's license, and violation of state law can result in fines or prison time.

How to voice his or her opinion. If a practitioner has especially strong views on the issue, it is his or her duty to make those views known to the legislative bodies addressing the issue. Evans says the single most effective means of doing so is joining local, state, and national professional organizations that have strong lobbying groups. Direct communication with legislators also is important, she says, as are education and encouragement of other professionals through continuing education and inservice training.

Reference

1. Evans E. Conscientious Objection: A Pharmacist's Right or Professional Negligence? *Am Jrl Health-System Phar* 2007;64(2):139-141. ■

Building a pharmacy system supported by hospital

For pharmacy to grow and compete in today's healthcare environment, the business culture of accounting and finance must be understood and embraced. For a service to be successful, the support of those who control the monetary resources is of primary importance, with support from physicians a distant second. That's the view of two pharmacy school professors who believe some, but not all, pharmacists must take the steps necessary to be able to bill for their services.

Writing an opinion piece in the *American Journal of Health-System Pharmacy*, **Ernest Dole**, PharmD., pharmaceutical care coordinator for internal medicine at Albuquerque's Gibson, Lovelace Medical Group, and clinical associate professor in the University of New Mexico Health Sciences Center College of Pharmacy and School of Medicine, and **Matthew Murawski**, PhD, associate professor of pharmacy administration at Purdue University, say that healthcare is no longer provided within a healthcare system, per se, but is instead a healthcare ecology.[1] They see healthcare provided within what they describe as a "dynamic network of alternative business models and institutions that are constantly created and modified and either thrive or die out. It is an evolutionary system that every day seems a little less likely to benefit from intelligent design. As with its biological counterpart, survival in the intensely competitive ecology of modern healthcare depends on fitness. And fitness, in what is ultimately a financial contest, is the ability to generate revenue."

The authors say that despite a sustained effort within the profession, pharmacists have been largely unsuccessful in securing the ability to bill for clinical services. Clinical services, they say, are subsidized to enhance patient outcomes, and cost avoidance of complex or costly therapeutic sequelae is assumed to justify the expense of sustaining those services. Ultimately, they say, clinical pharmacists do not typically bill for the services they provide. More than being simply an interesting historical artifact of the profession's development path, they fear that without substantial development of revenue-generating mechanisms, the profession's survival may be threatened. "If we are doing a purely clinical function and can't bill, we can't survive," Dole tells *Drug Formulary Review*. "The purely clinical function is in danger of going away."

Rethinking the 'bean counter' view

For a clinical pharmacy program to succeed, the authors say, the primary institutional support needed is financial administration. While clinical pharmacy has traditionally relied on physicians for support, the only way a change can take place, they say, is through understanding the culture of those in power. They argue that in most healthcare institutions today, physicians have relatively little power compared with the financial and business administration. "The power to make change lies within the jurisdiction of the chief operating officer and chief financial officer," they say. "Unfortunately, most clinicians look at the COO and CFO as 'bean counters' who do not understand the value of clinical pharmacy."

The report also notes that most clinical pharmacists don't have the tools needed to build a business case for their services. "While few would argue that reimbursement for pharmacists is an important topic, how many can say that they were taught how to build a service in terms that a finance person can understand?" they ask. "Most in the academic world will admit that they do not teach the use of financial data as a clinical tool. In a recent article surveying pharmacy residency training in academic settings, financial or business training was not listed as a concern."

While acknowledging the importance of pharma-

cists being able to bill, Mr. Dole and Mr. Murawski are clear that not all pharmacists should bill. They say that while many pharmacists perform well enough to justify billing for their services, there still would be many who are unable to do so. And the historic mechanism of state licensure is inadequate to meet this challenge, they contend. They feel no credentialing system currently exists for clinical pharmacists qualified to bill for their services. And in the absence of some system for differentiating those who can from those who should not, practitioners may be assigned responsibilities that exceed their expertise.

"The worst case scenario for the progress of pharmacists billing is that under Medicare Part D medication therapy management, pharmacists get in over their heads and someone gets hurt," the authors caution. "Then the profession would be set back for the next 25-30 years. In the beginning, pharmacists billing for their services should be an exclusive and not inclusive activity. Many system and professional barriers exist that prevent pharmacists from obtaining billing privileges: placing our primary emphasis on clinical outcomes versus financial outcomes, the current inability to train clinicians to use financial data as a clinical tool, incomprehension of the culture of those in power, and lack of any profession-wide credentialing system to ensure a minimum level of clinical expertise. Until these flaws are addressed, clinical pharmacy will make little progress in obtaining billing privileges and remain where it is today — a profession of second lieutenants, whining that no one lets us play while we refuse to learn the tools that will make us successful in the game."

[Editor's note: Contact Mr. Dole at (505) 262-3292.]

Reference

1. Dole E, Murawski, M. Reimbursement for clinical services provided by pharmacists: What are we doing wrong? Commentary *Am Jrl Health-System Phar* 2007; 64(1):104-106. ■

Pharmacist intervention ups heart medicine compliance

Heart-failure patients are more likely to comply with a medication regimen if they are under the continuing care of a pharmacist, according to a study from the University of North Carolina at Chapel Hill School of Pharmacy.[1]

The study evaluated 314 low-income patients with heart failure. One study group received typical services from a pharmacist, while the other group received care from a specially trained pharmacist who had access to customized educational materials, provided comprehensive instruction to participants, and reminded them to refill their prescriptions.

"For every $1 we spent on the intervention group, the healthcare system gained $14 in savings by decreasing emergency room visits and hospitalization," said UNC School of Pharmacy Mescal C. Ferguson Distinguished Professor **Michael Murray**, PharmD, the study's lead author.

Compared to patients in the control group, those who received special intervention took their medications 16% more consistently, visited the emergency room and were hospitalized 19% less, and had direct annual healthcare costs nearly $3,000 lower per patient. "The key to the success of our intervention was taking time with patients to create a regular schedule for taking their medicines that fit their lifestyle," said **James Young**, PharmD, the intervention pharmacist involved in the study at Wishard Health Services in Indianapolis. "We made sure that patients understood how their medications worked and why taking them consistently was so important."

The study investigators created special heart-specific materials designed to help patients with lower levels of health literacy. Thus, heart patients taking an ACE inhibitor received their pills in a bottle marked with an ace of hearts sticker. A corresponding user-friendly information sheet also was marked with the ace of hearts.

Researchers say that five million people in the U.S. have heart failure, with total healthcare costs more than $29 billion, largely from expensive exacerbations that require emergency visits and hospitalizations. Regularly administered cardiovascular medications may preserve cardiac function, improve quality of life, and reduce risk for costly exacerbations.

Researchers also have estimated that some 50% of patients with chronic illnesses do not take their medications as prescribed. Reasons for non-adherence include lack of patient knowledge, skills, and support to appropriately self-manage complicated medication regimens.

Few studies on interventions

While there are many chronic disease management programs, few studies have rigorously tested interventions aimed at improving patient adherence to prescribed medications and their effect on health outcomes.

In this study, the researchers hypothesized that the pharmacist intervention would improve adherence to heart failure medications, reduce exacerbations requiring emergency department visits or hospitalization, improve disease-specific quality of life, increase patient satisfaction, and reduce healthcare costs.

The primary study outcomes were medication adherence tracked by using electronic monitors and clinical exacerbations that required visits to the emergency department or hospitalization.

The study reports that the pharmacist intervention improved adherence to cardiovascular medications, including the proportion of medications taken, the reliability of scheduling these medications, and the amounts of medications refilled.

However, it said, the effects of the intervention on taking and scheduling adherence observed during the nine-month active intervention period dissipated in the three-month post-intervention period. Patients in the intervention group had fewer exacerbations requiring emergency room visits and hospital care and reported greater satisfaction with pharmacist services than did patients receiving usual care.

Costs of care were lower and improvements in disease-specific quality of life were greater in the intervention group but were not statistically significant.

With respect to costs, as more patients receive the intervention, the intervention development costs become negligible and the overall cost savings per patient approaches $3,000. "Indeed," the researchers said, "the return on investment in our study is $14 for every dollar spent on the intervention, which contrasts greatly from the return on investment of $6.50 for every dollar spent in a recent meta-analysis of more intensive post-discharge interventions in older adults with heart failure.

Reference

1. Murray MD, Young J, Hoke S. Pharmacist Intervention to Improve Medication Adherence in Heart Failure A Randomized Trial *Ann Intern Med* 2007; 146[10]: 714-725. ■

JCPP trying to turn vision 2015 into reality

The Joint Commission of Pharmacy Practitioners (JCPP) has approved an implementation plan for achieving its 2015 Vision for Pharmacy Practice. The commission said it expects its members to collectively pursue the vision in a robust manner. JCPP said it has begun the process for funding and implementing organizational changes needed to implement the vision.

Historically, the JCPP has served only as a forum where the volunteer leaders and CEOs of each of the nation's major pharmacy practitioner organizations meet face-to-face four times a year to discuss major items of mutual interest.

Over the past few years, the group has held planning discussions focused on patients' healthcare needs and pharmacists' role in meeting those needs. Out of that process came the vision for pharmacy practice in 2015. The vision states, "Pharmacists will be the healthcare professionals responsible for providing patient care

COMING IN FUTURE MONTHS

- Cost-sharing reduces statin adherence
- Using a prescription database in emergencies
- Bar-code technology helps medication administration
- Multidisciplinary approach to medication reconciliation
- How pharmacists reduce medication discrepancies

that ensures optimal medical therapy outcomes."

Achievement of this vision requires enhanced coordination and collaboration among the profession's practitioner organizations, JCPP said, and a commitment to focus and collaborate efforts toward implementation of pharmacist-provided patient focus care activities. Changes in JCPP's operational structure are expected to occur over the next several years.

Current JCPP members include: Academy of Managed Care Pharmacy; American College of Apothecaries, American College of Clinical Pharmacy, American Pharmacists Association, American Society of Consultant Pharmacists, American Society of Health-System Pharmacists, and National Community Pharmacists Association. Liaison members are American Association of Colleges of Pharmacy, Accreditation Counsel for Pharmacy Education; National association of Boards of Pharmacy; and National Council of State Pharmacy Associate Executives. ■

Joint Commission sets 2008 patient safety goals

Reducing risk of anticoagulant therapy added

Major changes in the Joint Commission 2008 National Patient Safety Goals include a new requirement to take specific actions to reduce the risks of patient harm associated with use of anticoagulant therapy and a new goal and requirement that address recognition of, and response to, unexpected deterioration in a patient's condition.

The new anticoagulant therapy requirement addresses a widely acknowledged patient safety problem and becomes a key element of the Goal to improve the safety of using medications, the Joint Commission said. It is applicable to hospitals, critical access hospitals, ambulatory care and office-based surgery settings, and home care and long-term care organizations.

The new goal and requirement on the deteriorating patient asks hospitals and critical access hospitals to select a suitable method for enabling caregivers to directly request and obtain assistance from a specially-trained individual if and when a patient's condition worsens. Full implementation of these provisions is targeted for January 2009, after a one-year phase-in.

Finally, the Joint Commission said, the requirement to limit and standardize drug concentrations that is part of the Goal to improve the safety of using medications will be retired as a National Patient Safety Goal, but organizational compliance will continue to be evaluated as part of the Medication Management standards.

A full text of the 2008 Goals and Requirements is available online at the Joint Commission web site at http://www.jointcommission.org. ■

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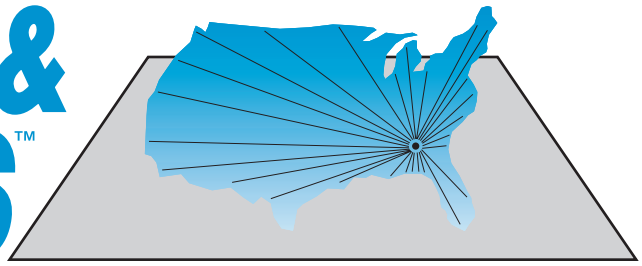

Under pressure: A review of pulmonary hypertension and its treatments

By **Karla Hinds**, Pharm. D. student at Auburn (Al) University,
[Editor's note: Hinds graduated from Auburn in May 2007.]

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder, but it is associated with high morbidity and mortality. Pulmonary arterial hypertension (PAH) affects about one to two people per million, usually those in the 20 to 30 year age range. Though treatment options have increased, the search for the ideal drug and/or combination therapy is an ongoing one for many patients with arterial hypertension.

Women are three times more likely than men to be diagnosed with PAH. Additional risk factors for PAH include portal hypertension or hepatic cirrhosis, pregnancy, obesity, cocaine abuse, use of oral contraceptives, fenfluramine, or dexfenfluramine, HIV infection, and genetic predisposition.[1] Due to the nonspecificity of initial symptoms, such as fatigue and shortness of breath, the average length of time from onset of symptoms to diagnosis is approximately two years. As the disease progresses, other symptoms can include dizziness on exertion, chest pain, and peripheral edema. At this time, there is an average survival time of 2.8 years after diagnosis.[2-3]

The diagnosis of IPAH is based on exclusion of other conditions, including COPD, left-sided heart disease, rheumatoid diseases, HIV, or liver disease. Other common etiologies of PAH are due to congenital heart defects or connective tissue disease. Right heart catheterization is required to confirm the diagnosis by measuring hemodynamic parameters.[2] According the American College of Chest Physicians (ACCP), PAH is defined as a sustained mean pulmonary arterial pressure (MPAP) greater than 25mmHg, or greater than 30 mmHg during exercise, and mean pulmonary capillary wedge pressure less than 15mmHg.[2-4]

Major advances in the treatment of IPAH have occurred in the past 30 years, with four new drug approvals since the year 2001.[2] Sitaxsentan, a selective endothelin receptor antagonist is the newest drug for the treatment of PAH in the pipeline.[5] **(See editor's note below.)** Available therapies for PAH are palliative, at best, and are not without consequence; therefore, it is important to carefully weigh the risks and benefits of each medication when choosing therapy. The treatment options for IPAH have increased tremendously in the past decade, and new treatments are still under development. For example, though no cure exists to date, epoprostenol has significantly increased the number of patients surviving to three years. Attempts to ease the delivery of this drug resulted in treprostinil and iloprost, which unfortunately did not show the same efficacy results as epoprostenol. Further studies should be conducted to determine if combination therapy with any of the available agents result in improved patient outcomes. The ideal drug would be one that targeted all pathological components of IPAH, could be orally-administered, and had few side effects. Until this product is developed, improved quality of life and increased survival time will remain the optimal level of treatment that can be provided for patients with IPAH.

Until recently, mainstays of treatment for IPAH included warfarin, calcium channel blockers (CCBs), digoxin, and diuretics. CCBs proved only to be efficacious in 10-25% of patients,[2-3] so treatments were quite limited for a vast majority of patients. Epoprostenol came to market in 1995,[2] and is now considered first-line therapy by the ACCP.[4] The

poor outcomes of the available treatments prompted research for drugs to correct the underlying pathophysiology of IPAH. Here is an update on some of the current options:

Calcium Channel Blockers: Once a diagnosis of PAH has been made, the patient's vasoreactivity should be measured.[2-4] ACCP guidelines recommend the use of IV epoprostenol, adenosine, or inhaled nitric oxide[4] for this trial due to risk of systemic hypotension and the long half-life associated with the use of CCBs for this testing.[2] Patients with PAH are classified as responders or non-responders based on the fall in MPAP when these drugs are administered. Responders have a fall in MPAP of at least 10 mmHg to less than or equal to 40 mmHg while maintaining cardiac output. Patients who are classified as "responders" show improved survival when treated with high-dose longterm oral CCB. One study by Rich, Kauffman, and Levy showed a 94% five-year survival rate in responders treated with high-dose CCBs as opposed to a 55% five-year survival rate in non-responders treated with diuretics, digoxin, and/or warfarin.[2,6]

The risk of systemic hypotension and decreased cardiac output associated with the use of high-dose CCBs can limit their utility, even in responders. If CCB therapy is indicated and deemed safe, a low to moderate dose of amlodipine, diltiazem, or nifedipine should be initiated, and titrated upwards as tolerated to a maximum dose of 40mg/day[6], 720 mg/day, or 120mg/day, respectively. Verapamil should be avoided due to its increased negative inotropic effects[2] and greater number of drug interactions when compared to other agents in its class.[2,4,6]

Warfarin: Patients with idiopathic PAH often have in *situ* thrombosis, as well as a higher risk of pulmonary thromboembolism due to right ventricular failure and venous stasis. Patients already possess compromised pulmonary circulation, and any obstruction in blood flow due to thrombus formation can greatly increase the risk of mortality. Another risk of thrombus associated with IPAH is catheter-associated when patients are treated with epoprostenol. Oral anticoagulation has been shown to increase the number of patients with IPAH surviving to three years; therefore, adults and children older than five years of age with IPAH should be treated with warfarin to a goal international normalized ratio (INR) of 1.5 to 2.5. Children less than five years of age should be treated to a lower goal INR. As with any medication, the benefit in warfarin therapy should outweigh the risk.[2,4] Routine monitoring should include signs and symptoms of bleeding, as well as routine INR measurement. Furthermore, patients should receive extensive counseling regarding adverse drug reactions, diet, and the importance of adherence to drug therapy and labwork.

Digoxin: Although digoxin has never been shown to have a long-term benefit in preventing mortality, it does have a niche in the treatment on IPAH. As previously mentioned, CCBs can have negative inotropic effects that can severely limit their utility in those with IPAH who are considered responders. The positive inotropic effects of digoxin can help to balance the effects of CCBs. Digoxin can also help to increase cardiac output in patients with right ventricular failure; however, the increased risk of sudden cardiac death should be carefully considered when determining if treatment with digoxin is warranted. Furthermore, hypoxemia, hypokalemia and renal insufficiency can also increase the risk of digoxin toxicity. Patients taking digoxin should be aware of the symptoms of toxicity, including nausea, vomiting, fatigue, and visual disturbances, and should be instructed to report to their health-care provider in the event of new onset of these symptoms.[2,4]

Diuretics: Fluid overload can be problematic in patients with IPAH and right ventricular failure. Diuretics can be used cautiously in this population to reduce peripheral edema and ascites and improve quality of life. However, excess diuresis can lead to decreased preload and decreased cardiac output resulting in systemic hypotension and compromised renal perfusion. Loop and thiazide diuretics are commonly used, but potassium-sparing diuretics are considered the agents of choice in IPAH. The choice of potassium-sparing diuretic is dependent upon whether or not the patient is concomitantly taking digoxin. Digoxin levels are altered when taken with spironolactone, but this drug interaction is not observed with triamterene; for this reason, triamterene is the preferred agent when a patient is taking digoxin. The renin-angiotensin-aldosterone system (RAAS) is commonly activated in IPAH due to increased filling pressure in the right heart. The ability of spironolactone to block the effects of the RAAS make it the preferred diuretic in patients not taking digoxin. If the use of monotherapy with these agents does not result in the desired diuresis, a loop diuretic may be added to the medication regimen. Renal function, fluid status, electrolytes (especially potassium), and blood pressure should be carefully assessed on a regular basis in patients with IPAH treated with diuretics.[2]

Prostacyclin Analogs: Continuous IV infusion of epoprostenol, a synthetic analog of prostacyclin has been demonstrated to have long-term efficacy in IPAH, and is considered an alternative to transplant. It is FDA approved for the treatment of IPAH associated with NYHA functional class III or IV symptoms. Epoprostenol decreases MPAP and PVR, while it increases cardiac output, exercise tolerance, quality of life, and survival. There is also some evidence to suggest that long-term treatment with epoprostenol can reverse some of the vascular remodeling seen with IPAH. Optimal dosing of epoprostenol is one that minimizes side effects and tachyphylaxis while maintaining efficacy. Studies have determined that this dose must be individualized to the patient periodically during right heart catheterization, and adjusted to a target cardiac index of 2.5-4 L/minute/m^2.[2,2] There is clearly a marked benefit associated with epoprostenol, which has led to the ACCP recommendation that epoprostenol be considered first-line therapy for IPAH in patients who do not respond to treatment with CCBs.[4] There are, however, some significant downfalls to epoprostenol therapy. Firstly, because epoprostenol has a half-life of three to five minutes and no oral bioavailability, it must be administered via continuous IV infusion, requiring the placement of an indwelling subclavian or jugular catheter and the use of a portable infusion pump. Patients and their caregivers must also be instructed on mixing the drug using aseptic technique. Furthermore, epoprostenol must be protected from heat and light, so it must be stored in a container with an ice pack to maintain the integrity of the drug. This complicated drug delivery system puts the patient at risk of a pulmonary hypertensive emergency should therapy be interrupted, catheter-associated thrombus or infection, sepsis, and even death should these events occur. All of the aforementioned ADRs are in addition to those associated with the class, including nausea, headache, flushing, and jaw pain.[2,4] The ACCP recommends that clinical centers of excellence manage these patients so as to prevent these complications.[4] In attempts to overcome the burden of administering epoprostenol, two other prostacyclin analogs have been introduced to the market in the past five years. Treprostinil, given as a continuous subcutaneous infusion, is FDA approved for IPAH with NYHA functional class II to IV symptoms to improve exercise capacity; and iloprost, a nebulized inhalation, is FDA approved for IPAH with NYHA class III to IV symptoms. The advantages of treprostinil are its increased half-life (two to four hours) and its stability at room temperature. Furthermore, the subcutaneous infusion device is much like an insulin pump, and involves far fewer risks. Benefits of treatment with iloprost include the local administration of the drug, which limits ADRs related to systemic administration. It also has a longer duration of action than that of epoprostenol, with effects lasting from 60-120 minutes. This allows the patient to have a 10-minute nebulizer treatment six to nine times daily.[2] An oral formulation of prostacyclin has been used in Japan, but has not been pursued for FDA approval in the United States.[2] Although there are decreased risks associated with the use of these newer prostacyclin analogs, they have not been proven to be as effective in treating IPAH as epoprostenol; therefore, ACCP recommends that these agents be considered second-line therapies.[4]

Endothelin Receptor Antagonists: Bosentan (Tracleer™) is the only endothelin receptor antagonist available, and is FDA approved for the treatment of IPAH with NYHA class III or IV symptoms. It non-selectively inhibits the effects of endothelin on ET-A and ET-B, and causes a reduction in vasoconstriction and vascular remodeling. Improvements in exercise capacity, hemodynamics, and functional class have been demonstrated in clinical trials. Furthermore, bosentan is administered orally as a twice-daily dose,[2] and is considered a first-line therapy for IPAH in those who are considered "non-responders" to CCBs.[4] Bosentan contains a black box warning concerning the risk of teratogenecity and liver toxicity. The liver toxicity is associated with elevated liver transaminases and increased total bilirubin, is dose-dependent, and reversible upon discontinuation of the drug.[7] Nonetheless, treatment with bosentan does require frequent monitoring of liver enzymes and enrollment in the TracleerTM Access Program, a distribution and reimbursement program.[8]

Phosphodiesterase Inhibitors: Sildenafil (Revatio™) is commonly known by the trade name Viagra ™ for the indication of erectile dysfunction. It works by inhibiting the type-5 phosphodiesterase receptor, thus increasing levels of cyclic guanosine monophosphate, a potent vasodilator in pulmonary and penile tissues.[1] Sildenafil is FDA approved to increase exercise capacity in patients with NYHA class II-IV symptoms, and is the newest treatment for IPAH.[2,10] Sildenafil has shown substantial improvement in hemodynamics and exercise tolerance during clinical studies with little systemic hypotension, and the SUPER-1 and 2 trials indicate that there

might be a long-term mortality benefit with its treatment. Sildenafil has also been shown to be beneficial when used in combination with bosentan or prostacyclin analogs.[2] Dosing of sildenafil for IPAH is 20 mg three times daily by mouth, and the most common adverse reactions are headache, visual disturbances, and nasal congestion.[10] Currently, the ACCP recommends that sildenafil be used only when patients do not qualify for other treatments, or other therapy fails.[4] It should be noted, however, that the most recent ACCP recommendations were published in 2004,[4] and sildenafil was FDA approved for IPAH in 2005.[2] With official FDA approval and more clinical trials available, ACCP will likely update their recommendations to include use of sildenafil as first-line monotherapy for mild cases of IPAH and its use in combination therapy for severe cases.[10]

[Editor's note: On June 15, 2007 the Food and Drug Administration advised Encysive Pharmaceuticals that its development program for sitaxsentan (Thelin) did not demonstrate the evidence of effectiveness needed for approval. The company recently met with the FDA and was expected to file a request for a formal dispute resolution as this issue went to press.]

References:

1. Raissy HH, Harkins M, Marshik PL. Drug-Induced Pulmonary Diseases. In: Dipiro, JT, Talbert RL, Yee GC, et al, editors. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 587-8.

2. Hackman AM and Lackner TE. Pharmacotherapy for Idiopathic Pulmonary Arterial Hypertension During the Past 25 Years. Pharmacotherapy. 2006;26(1):68-94.

3. Benza RL, Mehta S, Keogh A, et al. Treatment for Patients with Pulmonary Arterial Hypertension Discontinuing Bosentan. *J Heart Lung Transplant*.2007;26:63-9.

4. Badesch DB, Abman SH, Ahearn GS, et al. Medical Ther apy for Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. *Chest*. 2004; 126(1):35s-63s.

5. Drug Information Department. Encysive Pharmace uticals Houston, TX. March 21, 2007.

6. Robbins I. The Role of Calcioum Channel Blockers in Pulmonary Arterial Hypertension. *Medscape Cardiology* [serial online]. 2006;10(1). Available at: http://www.med scape.com/viewarticle/523338. Accessed March 29, 2007.

7. Tracleer [package insert]. San Francisco, CA: Actelion Pharmaceuticals US, Inc.; 2001.

8. Tracleer website. Available at: www.tracleer.com. Accessed March 18, 2007.

9. Benedict NJ. Sitaxsentan in the Management of Pulmon ary Arterial Hypertension.*Am J Health-Syst Pharm*.2007;64:363-8

10. Sildenafil. DrugDex Evaluations [database online]. Greenwood Village, CO. Thomson Micromedex; Accessed March 29, 2007. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

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- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
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5. Pulmonary arterial hypertension affects about one to two people per million, usually those in what age range?
   A. 10 years and younger
   B. Teenagers
   C. 20 to 30 years old
   D. Over 65 years

6. The ideal drug for idiopathic pulmonary arterial hypertension (IPAH) would be one that:
   A. Targeted all pathological components
   B. Could be orally-administered
   C. Had few side effects
   D. All of the above

7. Loop and thiazide diuretics are commonly used, but potassium-sparing diuretics are considered the agents of choice in IPAH. The choice of potassium-sparing diuretic is dependent upon whether or not the patient is concomitantly taking:
   A. Warfarin
   B. Calcium channel blockers
   C. Digoxin
   D. None of the above

8. Citing efficacy problems, the FDA declined to approve sildenafil for IPAH in a 2005 ruling.
   A. True
   B. False

The continuing education questions in the July issue of Drug Criteria & Outcomes should have been numbered 1-4 rather than 25-28. We resume correct numbering in this issue with questions 5-8. We apologize for any confusion caused by the error.