Emerging Solutions in Pulmonary Arterial Hypertension

Empowering Pharmacists in Treatment Decisions

Monday, December 3, 2012
7:30 – 8:30 AM
Las Vegas, NV

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Educational Overview

Pulmonary arterial hypertension (PAH) is a rare disease with significant consequences, including serious functional impairment and premature death. If left untreated, PAH is rapidly fatal. Fortunately, over the past decade, the knowledge and understanding of this disease has greatly expanded. Furthermore, the availability of effective and more convenient oral and inhaled medications has allowed clinicians to better individualize therapy to meet patient treatment goals. Though there is no cure for PAH, effective treatment can significantly slow disease progression and clinical worsening. Given the serious nature of this disease and its rapid progression, optimal management approaches are essential.

The Role of the Pharmacist

Optimal management of patients with PAH requires early detection and diagnosis followed by a patient-centered treatment plan. By increasing their competency, pharmacists can play an important role within the multidisciplinary team when encountering patients with this disease.

Given the complex and individualized nature of PAH therapy, pharmacists must have a full understanding of treatment algorithms, disease-specific therapies, and long-term monitoring recommendations based on evidence-based guidelines. As the armamentarium to treat PAH continues to expand, pharmacists must make efforts to stay informed of the latest finding in order to contribute to the optimal management of these patients.

Target Audience

This continuing pharmacy education activity is planned to meet the needs of pharmacists in a variety of practice settings, including large and small healthcare systems, outpatient clinics, managed care organizations, long-term care facilities, and academia. This program targets health-system pharmacists who are responsible for the safe and effective use of medications utilized for the treatment of patients with PAH.

Learning Objectives

Upon completing this activity, participants will be able to:

• Differentiate the safety and efficacy among the various classes of medications used in the treatment of PAH

• Utilize evidence-based guidelines to select appropriate therapy to meet individualized patient treatment goals

• Optimize management decisions based on pathophysiology of PAH

• Discuss the role of clinical pharmacists in the management of patients with PAH
# Educational Program

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:30 – 7:35 AM</td>
<td>Managing Patients with PAH: Where to Start?</td>
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<tr>
<td></td>
<td>David Badesch, MD</td>
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<tr>
<td>7:35 – 8:05 AM</td>
<td>Utilizing Current Therapeutic Options and Treatment Algorithms to Optimize Outcomes</td>
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<td>David Badesch, MD</td>
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<tr>
<td>8:05 – 8:25 AM</td>
<td>Individualizing Therapy to Meet Patient Goals: Recognizing the Pharmacist’s Role</td>
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<td>James Coons, PharmD</td>
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<td>8:25 – 8:30 AM</td>
<td>Open Forum: Q&amp;A</td>
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</table>

## Faculty

### David B. Badesch, MD, FACP, FCCP

- Professor of Medicine
- Divisions of Pulmonary Sciences, Critical Care Medicine and Cardiology
- Clinical Director, Pulmonary Hypertension Center
- University of Colorado at Denver and Health Sciences Center
  - Denver, CO

### James C. Coons, PharmD, BCPS (AQ Cardiology)

- Associate Professor
- University of Pittsburgh School of Pharmacy
- Cardiology Residency Program Director
- Clinical Pharmacist, Cardiology
- University of Pittsburgh Medical Center-Presbyterian Hospital
  - Pittsburgh, PA
**Accreditation**

**Pharmacists**

Center for Independent Healthcare Education is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. Center has assigned 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credits for participating in this activity.

**ACPE UAN:** 0473-9999-12-007-L01-P

**Type of Activity:** Knowledge-based

**Instructions for Credit**

To receive a Statement of Credit, participants must register for the symposium, document attendance, and complete and return the evaluation form. You can access information about your completed CPE through MyCPEmonitor.net.

**Disclosure of Conflicts of Interest**

In accordance with policies set forth by the Accreditation Council for Continuing Medical Education (ACME) and the Accreditation Council for Pharmacy Education (ACPE), Center for Independent Healthcare Education requires all faculty members and spouses/significant others with an opportunity to affect the content of a continuing education activity to disclose any relevant financial relationships during the past 12 months with commercial interests. A commercial interest is any entity producing, marketing, reselling or distributing healthcare goods or services consumed by or used on patients. Relationships with commercial interests and conflicts of interest resulting from those relationships must be revealed to the audience and resolved prior to the activity.

Relevant relationships include roles such as speaker, author, consultant, independent contractor (including research), employee, investor, advisory committee member, board member, review panelist, and investigator. If a potential speaker or author indicates a possible conflict of interest, the conflict will be resolved by choosing another speaker or author for that therapeutic area, or the slides, handouts, and/or monograph will be reviewed and approved by a qualified commercially-disinterested peer.

**Financial Interest Summary**

David B. Badesch, MD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Advisory Board/Steering Committees: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, Ikaria, Arena
- Consultant: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, Ikaria, Arena
- Grant Recipient/Research Support: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Novartis, Bayer, Ikaria, Arena

Dr. Badesch does not intend to discuss the off-label use of a product.

James C. Coons, PharmD (Faculty/Planner) has no relevant financial relationships with commercial interests. Dr. Coons does not intend to discuss the off-label use of a product.

No other speakers, authors, planners or content reviewers have any relevant financial relationships to disclose. No other speakers or authors will discuss off-label use of a product.

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**Commercial Support**

This activity is supported by an educational grant from Actelion Pharmaceuticals, US, Inc.
Utilizing Current Therapeutic Options and Treatment Algorithms to Optimize Outcomes

David B. Badesch
MD, FACP, FCCP
Dr. David Badesch is Professor of Medicine, in the Divisions of Pulmonary Sciences and Critical Care Medicine, and Cardiology, and Clinical Director of the Pulmonary Hypertension Center, at the University of Colorado at Denver and Health Sciences Center (UCDHSC). He is also a Distinguished Advisor to the Scientific Leadership Council of the Pulmonary Hypertension Association (PHA) and a member of the Pulmonary Vascular Research Institute (PVRI).

Dr. Badesch received his undergraduate degree in Mathematics from Vanderbilt University in Nashville, TN and then went on to complete his medical degree from the University of Virginia School of Medicine, Charlottesville, VA. After completing his residency in Internal Medicine from Vanderbilt University School of Medicine, he went to complete a fellowship in Pulmonary Medicine from the University of Colorado School of Medicine, Denver, CO. He is board certified in Internal Medicine with a subspecialty in Examination in Pulmonary Diseases.

Dr. Badesch has published in numerous journals including the *Annals of Internal Medicine*, *New England Journal of Medicine*, *Lancet*, *Journal of the American College of Cardiology*, and *CHEST*. He serves as a reviewer for several scientific publications including the *American Review of Respiratory Diseases*, *Annals of the Rheumatic Diseases* and *Arthritis and Rheumatism*. Dr. Badesch is a fellow of the American College of Chest Physicians (ACCP) and the American College of Physicians (ACP) and a member of the American Thoracic Society (ATS). He serves on the Steering Committees (national and international) of many of the major clinical trials conducted in the field of pulmonary hypertension. Dr. Badesch has been listed among the Best Doctors in America 2001-2010.
Pulmonary Arterial Hypertension

Key Points:
• Non-specific symptoms → delayed diagnosis
• Poor prognosis without therapy
• Methodical evaluation, including catheterization required
• Evolving therapies → improved prognosis (but not yet normal)

A Disease of Decline and Deterioration: IPAH Survival if Untreated

- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

PAH: Hemodynamic and Clinical Course

McLaughlin VV et al. Chest. 2004;126:78S-91S.
Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH
   • Idiopathic PAH
   • Heritable
   • Drug- and toxin-induced
   • Persistent PH of newborn
   • Associated with:
     - CTD
     - HIV infection
     - Portal hypertension
     - CHD
     - Schistosomiasis
     - Chronic hemolytic anemia

2. PH Owing to Left Heart Disease
   • Systolic dysfunction
   • Diastolic dysfunction
   • Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia
   • COPD
   • ILD
   • Other pulmonary diseases with mixed restrictive and obstructive pattern
   • Sleep-disordered breathing
   • Alveolar hypoventilation disorders
   • Chronic exposure to high altitude
   • Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
   • Hematologic disorders
   • Systemic disorders
   • Metabolic disorders
   • Others


REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata

PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis

Is There a Reason to Suspect PAH?

**Clinical Presentation**

<table>
<thead>
<tr>
<th>Common Initial Symptoms</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>13</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5</td>
</tr>
<tr>
<td>Leg edema</td>
<td>3</td>
</tr>
</tbody>
</table>


**Diagnostic Approach**

- RVE, RAE, TRVSP
- Left heart disease
- VHD
- CHD

- Echocardiogram
- CXR
- ECG
- PFTs
- Sleep disorder
- Sleep study

- LFTs and clinical evidence of cirrhosis and portal hypertension

- HIV test
- Autoantibody tests
- Ventilation-perfusion scan, Contrast CT, Angiography
- Scleroderma
- SLE
- RA
- Vasculitis
- Chronic thromboembolism

- Portopulmonary hypertension
- HIV
- RH cath
- Vasodilator test


**Dana Point Hemodynamic Definition of PH/PAH**

- PH: Mean PAP ≥25 mm Hg

- PAH: Mean PAP ≥25 mm Hg plus PCWP/LVEDP ≤15 mm Hg

PH: The Importance of Hemodynamics

Pulmonary venous hypertension
Elevated PCWP, normal PVR

PAH
PH with respiratory disease
CTEPH
Normal PCWP, elevated PVR

Cardiac Catheterization

• Exclude congenital heart disease
• Measure wedge pressure or LVEDP
• Establish severity and prognosis
• Test vasodilator therapy

Catheterization is required when pulmonary hypertension is suspected

PAH Treatment Goals

• Fewer/less severe symptoms
• Improved exercise capacity
• Improved hemodynamics
• Prevention of clinical worsening
• Improved quality of life
• Improved survival
**What Is the Optimal Treatment Strategy?**

<table>
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<tr>
<th>Anticoagulate ± Diuretics ± Oxygen ± Digoxin</th>
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<tr>
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<td>Yes</td>
<td></td>
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<td>Continue CCB</td>
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</table>

**Lower Risk Determinants of Risk**

- No Clinical evidence of RV failure
- Gradual Progression of symptoms
- WHO class II, III
- Longer (>400 m) 6MWD
- Peak VO<sub>2</sub> ≤10.4 mL/kg/min
- Minimal RV dysfunction

**Higher Risk Determinants of Risk**

- Yes Clinical evidence of RV failure
- Rapid Progression of symptoms
- WHO class IV
- Shorter (<300 m) 6MWD
- Peak VO<sub>2</sub> >10.4 mL/kg/min
- Minimal RV dysfunction

**Other Management Issues**

- Encourage exercise and activity within the limits of disease and ability to maintain O2 levels
- Immunizations
- Contraception

**What Is the Optimal Treatment Strategy?**

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- Peak VO<sub>2</sub> >10.4 mL/kg/min
- Minimal RV dysfunction

Calcium Channel Blockers
Only If “Vasodilator Responsive”

“Vasodilator Response”
- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO


Survival in IPAH
Long-term CCB Responders

Long-term CCB responders (~50% of acute responders or ≤6% of IPAH patients)

Long-term CCB failure


What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Negative

Oral CCB

Sustained Response

No

Yes

LOWER RISK
- No Clinical evidence of RV failure
- Gradual Progression of symptoms
- WHO class II, III
- 6MWD Longer (>400 m)
- Peak VO2 >10.4 mL/kg/min
- Echocardiography: Minimal RV dysfunction
- Hemodynamics: RAP <10 mm Hg; CI >2.5 L/min/m²
- BNP Minimal elevated

HIGHER RISK
- Clinical evidence of RV failure
- Rapid Progression of symptoms
- WHO class IV
- 6MWD Shorter (<300 m)
- Peak VO2 <10.4 mL/kg/min
- Echocardiography: Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement
- Hemodynamics: RAP >20 mm Hg; CI <2.0 L/min/m²
- BNP Significantly elevated

Approved Therapeutic Targets

- Endothelin Pathway
- Nitric Oxide Pathway
- Prostacyclin Pathway

- Pre-proendothelin → Proendothelin → Endothelin-1
- L-arginine → L-citrulline
- Endothelial cells → Arachidonic acid → Prostaglandin
- Endothelin receptor A & B
- Endothelial nitric oxide synthase (eNOS)
- Phosphodiesterase type 5 inhibitor
- Exogenous nitric oxide
- Endothelin receptor antagonists


IV Epoprostenol in IPAH: Change From Baseline in 6MWD

- Epoprostenol (n=41; baseline=315 m)
- Conventional (n=40; baseline=270 m)

- Median change from baseline (m)
  - Epoprostenol: 31
  - Conventional: -29
  - p<0.002


IV Epoprostenol in PAH Due to Scleroderma: Change From Baseline in 6MWD

- Conventional therapy (n=55)
- Epoprostenol (n=56)

- Median change from baseline (m)
  - Week 1: p=0.003
  - Week 6: p=0.001
  - Week 12: p<0.001

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy

Epoprostenol (n=41) vs Conventional therapy (n=40)

*p=0.003*

Two-sided, by log-rank test.


Subcutaneous Treprostinil: Change From Baseline in 6MWD Overall and by Dose Quartile

Mean change from baseline (m)

Placebo: overall (n=236) vs Treprostinil: overall (n=233)

By Dose Quartile

1st 5 - <8.2 8.2 - <13.8 >13.8

Mean dose (ng/kg/min)

Hodges-Lehmann estimate


Treprostinil IV: 6MWD (TRUST)

Mean 6MWD (m)

Placebo (n=14) vs Treprostinil IV (n=30)

*p=0.022. 6MWD values are mean±SE.

Inhaled Iloprost: Change From Baseline in 6MWD (AIR Trial)

6MWD was not the primary end point in the AIR trial.


Inhaled Treprostinil: Median Change in 6MWD (TRIUMPH)

Hodges-Lehmann estimate of treatment effect.

Peak: between 10-60 min after dose. Trough: 4 hr after dose.


Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

Vary according to drug and route of delivery
Approved Therapeutic Targets

Nitric Oxide Pathway
Endothelial cells
Pre-proendothelin
Proendothelin

Endothelin-1
L-arginine
L-citrulline
Protcyclin
Prostanadion G (prostacyclin)

Endothelial cells
Proendothelin
Arachidonic acid
Prostanadion E
Endothelin receptor A
Endothelin receptor B

Endothelium
Endothelial cells
Smooth muscle cells

Exogenous nitric oxide
Phosphodiesterase type 5 inhibitor


Bosentan: 6-MWD (351 and BREATHE-1)

Study 351

Bosentan
(n=21)

Placebo
(n=11)

Week
Baseline 4 8 12 20

BREATHE-1

Bosentan
(n=144)

Placebo
(n=69)

Week
Baseline 4 8 16

*p<0.05 vs baseline; **p=0.021 vs placebo. Values are mean ± SEM.


Bosentan: Time to Clinical Worsening (BREATHE-1 and EARLY)

BREATHE-1

89%
p=0.0038

63%
p=0.0015

EARLY

77%
p=0.0114

Patients with no clinical worsening

Time (wk)

Notes:
Would Earlier Treatment Be Better?
The “EARLY” Study


Ambrisentan in PAH: 6MWD (ARIES)


Ambrisentan in PAH: Time to Clinical Worsening (ARIES)

Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function
  - reversible transaminase elevations >3X ULN
  - may require dose adjustments or discontinuations
  - monthly LFTs required
- Edema
  - lower extremity edema may require diuretic adjustment
- Use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets


Effect of Sildenafil on 6MWD (SUPER)

Sildenafil: Incidence of Clinical Worsening (SUPER)

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence, n (%)</th>
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<tbody>
<tr>
<td>Clinical worsening</td>
<td>Placebo (n=70)</td>
</tr>
<tr>
<td>- death</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- hospitalization for PAH</td>
<td>7 (10)</td>
</tr>
<tr>
<td>- initiation of prostacyclin</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- initiation of bosentan</td>
<td>0</td>
</tr>
</tbody>
</table>


Effect of Tadalafil* on 6MWD (PHIRST)

*Adcirca®

Effect of Tadalafil on Time to Clinical Worsening (PHIRST)

**PDE-5 Side Effects**
- Nose bleed
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes
- Contraindicated with use of nitrates

**What Is the Optimal Treatment Strategy?**

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<th>Diuretics</th>
<th>Oxygen</th>
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<tbody>
<tr>
<td><strong>Positive</strong></td>
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<tr>
<td><strong>Negative</strong></td>
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**LOWER RISK DETERMINANTS OF RISK**
- No
- Clinical evidence of RV failure

**INTERMEDIATE RISK**
- Gradual progression of symptoms
- WHO class II, III

**HIGHER RISK**
- Rapid
- WHO class IV

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>Longer (&gt;400 m)</td>
<td>GMWD</td>
</tr>
<tr>
<td>Peak VO₂ &gt;10.4 mL/kg/min</td>
<td>CPET</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg; CI &gt;2.5 L/min/m²</td>
<td>Hemodynamics</td>
</tr>
<tr>
<td>Minimally elevated BNP</td>
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**ACCF/AHA Consensus PAH Treatment Algorithm**

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</table>

**Lower Risk**
- ERAs or PDE-5 Is (oral)
- Epoprostenol or Treprostinil (IV)
- Iloprost (inhaled)
- Treprostinil (SC, inhaled)

**Investigational Protocols**
- Atrial septostomy
- Lung transplant


French Registry: Kaplan-Meier Survival Estimates According to Baseline NYHA Functional Class

![Graph showing survival estimates for NYHA functional classes I/II, III, and IV over time.]

No. at risk:
- NYHA I/II: 12, 15, 19, 23, 24, 26, 27
- NYHA III: 37, 48, 70, 79, 86, 88, 89
- NYHA IV: 7, 6, 9, 11, 10, 13, 17

Combined idiopathic, familial, and anorexigen-associated PAH.

French Registry: Kaplan-Meier Survival Estimates According to Baseline 6MWD

![Graph showing survival estimates for different 6MWD categories: ≥350 m, 250-349 m, 0-249 m over time.]

No. at risk:
- 0-249: 17, 19, 29, 30, 28, 32, 35
- 250-349: 16, 19, 21, 27, 31, 33, 35
- ≥350: 17, 23, 37, 45, 50, 52, 53

Combined idiopathic, familial, and anorexigen-associated PAH.

Plasma BNP as a Prognostic Indicator in Patients With IPAH

![Graph showing survival rates for different BNP levels over time.]

Follow-up BNP
- BNP <180 pg/mL
- BNP ≥180 pg/mL

Survival rates (%)

Time (mo)

By multivariate analysis, higher BNP at follow-up (RR = 25.880, p = 0.0243) was an independent predictor of mortality.

Sildenafil Added to Epoprostenol (PACES)


**Combination Therapy: Other Ongoing or Recently Completed Clinical Trials**

<table>
<thead>
<tr>
<th>Current therapy</th>
<th>Added therapy</th>
<th>Patients (n)</th>
<th>Study duration</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEDOM-C</td>
<td>Bosentan and/ or sildenafil</td>
<td>Treprostinil oral</td>
<td>300</td>
<td>16 weeks</td>
</tr>
<tr>
<td>AMBITION</td>
<td>Bosentan</td>
<td>Ambrisentan/ tadalafil/combo</td>
<td>100</td>
<td>Event-driven</td>
</tr>
<tr>
<td>Pifer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
</tr>
<tr>
<td>COMPASS-1</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>45</td>
<td>Single dose</td>
</tr>
<tr>
<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
<td>Event-driven</td>
</tr>
<tr>
<td>COMPASS-3</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>100</td>
<td>16 weeks</td>
</tr>
<tr>
<td>ATHENA-1</td>
<td>Sildenafil or tadalafil</td>
<td>Ambrisentan</td>
<td>40</td>
<td>24 weeks</td>
</tr>
<tr>
<td>SERAPHIN</td>
<td>Sildenafil</td>
<td>Macitentan</td>
<td>742</td>
<td>Event-driven</td>
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<tr>
<td>PATENT</td>
<td>Naive/PGI/ERA</td>
<td>Riociguat</td>
<td>462</td>
<td>12 weeks</td>
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<tr>
<td>IMPRES</td>
<td>Naive/5 current therapies</td>
<td>Imatinib</td>
<td>200</td>
<td>24 weeks</td>
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<tr>
<td>ATRAPPS</td>
<td>Ambrisentan/ tadalafil/combo</td>
<td>Combo vs mono</td>
<td>62</td>
<td>36 weeks</td>
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<tr>
<td>GRIPHON</td>
<td>ERA, PDE5 or both</td>
<td>Sildenafil</td>
<td>670</td>
<td>Event-driven</td>
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**It Takes a Team**

A truly multidisciplinary approach

- Pulmonary
- Cardiology
  - Cath Lab Team
  - Echo
  - Congenital Heart Disease
- Rheumatology
- Interventional Radiology
- Pharmacy
- Nursing
- Research
  - COMIRB
  - CCTSI
  - HHRC
- Respiratory Therapy
- Cardiothoracic Surgery / Lung Transplantation
- Hepatology / Transplant Surgery / Liver Tx
- Pediatric PH Program at Children’s Hospital Colorado
- Basic and translational research
Individualizing Therapy to Meet Patient Goals: Recognizing the Pharmacist’s Role

James C. Coons
PharmD, BCPS (AQ Cardiology)
Dr. James Coons is an Associate Professor, Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy in Pittsburgh, PA. After receiving his Doctor of Pharmacy from the University of Pittsburgh, he completed a PGY-1 residency in pharmacy practice at the University of Virginia Health System in Charlottesville, VA. This was followed by a PGY-2 specialty residency in cardiology pharmacy practice at the University of Pittsburgh.

Until August 2012, Dr. Coons was a clinical pharmacy specialist in cardiology at Allegheny General Hospital in Pittsburgh. During that time, he managed patients in the cardiac intensive care unit and those under the care of the advanced heart failure service. He also served as the PGY-1 residency program director.

Dr. Coons’ research interests focus on the optimal use of antiplatelets and anticoagulants in the setting of acute coronary syndromes and percutaneous coronary intervention, as well as the application of pharmacogenomics in improving outcomes in this patient population.
Objective:
Discuss the role of clinical pharmacists in the management of patients with PAH.

Case Presentation: Meet CJ

- CC/HPI: CJ is a 33-year-old female who presents to the PH clinic with c/o progressive dyspnea and fatigue x 3 weeks with 15 lbs. weight gain since last visit (3 months ago). Symptoms noted with minimal activities.

- PMH: idiopathic PAH (diagnosed at age 29 yrs), GERD, type 2 diabetes mellitus, depression

- Meds: sildenafil 20 mg tid, bosentan 125 mg bid, omeprazole 20 mg qd, glyburide 5 mg bid, metformin 500 mg bid, sertraline 50 mg qd

Case Presentation

- Pertinent labs (1 week ago):
  BUN/SrCr: 40/1.6 mg/dL (20/1.1 at last visit)
  NT-proBNP: 800 pg/mL

- Vital signs: BP: 95/50 mmHg; HR: 110 bpm

- Current weight: 80 kg

- 6MWD: 280 meters (440 meters at last visit)

- Plan: Admit for right heart catheterization (RHC) and possible initiation of prostacyclin therapy
Case Presentation

• Summary of RHC findings:
  PAP: 80/40 mmHg (mPAP: 53 mmHg)
  CI: 1.9 L/min/m²
  PvO₂: 50%
  PCWP: 12 mmHg; CVP: 15 mmHg
  SVR: 1250 dynes × sec/cm⁵
  PVR: 1025 dynes × sec/cm⁵

• Next steps:
  – Admit to cardiac ICU for initiation of
    IV epoprostenol at 2 ng/kg/min continuous IV infusion
Current Challenges in PAH Care

• Expansion of therapeutic options
  – Medications
  – Delivery systems

• Complexity of regimens

• High-risk medications

• Patient acuity

• Educational needs

Considerations by Medication

Epoprostenol

• Requires reconstitution

• Requires back-up cassette

• Multiple formulations
  – Epoprostenol (Flolan®)
  – Generic epoprostenol
  – “Room-temperature stable” epoprostenol (Veletri®)

Considerations by Medication

Epoprostenol (Veletri®)

• Not bioequivalent to Flolan® or generic

• Improved stability

• Reconstitute with sterile water or 0.9% sodium chloride, not sterile diluent for epoprostenol
Considerations by Medication

Treprostinil (Remodulin®)
- Multiple vial concentrations
  - 1, 2.5, 5, & 10 mg/mL
- Multiple routes of administration
  - IV, SC, inhaled
- Multiple delivery systems
  - IV – CADD® infusion pump, Crono-5® pump
  - SC – CADD-MS3® & Mini-Med® syringe pumps
  - Inhaled – Tyvaso inhalation system®

Parenteral Treprostinil Delivery

IV CADD
- Continuous IV infusion
- Titration
- Requires dilution
- Rate provided in mL/day
- 48 hour stability

CRONO-5
- Continuous IV infusion
- Not generally for titration
- Requires dilution
- Stable doses of medication
- 20 mL syringe
- Rate provided in mL/hr
- 48 hour stability

SC
- Continuous SC infusion
- CADD-MS3®
- Mini-Med 407c® (being phased out)
- Not diluted
- Rate provided in mL/hr
- 72 hour stability

Inhalational Treprostinil Delivery

Treprostinil (Tyvaso®)
- Supplied as foil packs
  - Each pack contains 4 ampules
  - 1 ampule (1.74 mg/2.9 mL)
  - 1 ampule per day regardless of total dose
  - Opened foil pack stable for 7 days
- Dispense as multi-dose vs. single-dose?
Considerations by Medication

**Endothelin-1 Receptor Antagonists**

- Special enrollment
  - Bosentan (Tracleer®)
    - Tracleer Access Program (T.A.P.)
  - Ambrisentan (Letairis®)
    - Letairis Education and Access Program (L.E.A.P.)
- New initiation vs. maintenance

Scope of Problem

- Surveys of PAH centers
  - University Hospital Consortium (UHC)
  - Phone interview – 18 large PAH centers
  - Electronic survey – convenience sample of all PAH centers in US (n =97)


Scope of Problem

- UHC and phone interviews
  - Baseline evaluation of policies
    - 8 of 18 kept patients on their home pumps
    - 10 of 18 patients did not keep back-up prostacyclin cassettes on the unit

Scope of Problem

• Phone interview
  – Serious errors at 17 of 18 centers
    • Failure to restart CADD pump
    • Wrong patient
    • Wrong rate
    • Errors in dose calculations
    • Flushing of the prostacyclin line
  – 3 deaths


Scope of Problem

• Electronic survey
  – Serious or potentially serious errors – 68%
    • Wrong patient
    • Wrong dose
    • Pump left off
    • Flushing the line
  – 9 deaths


Role of the Pharmacist

• Medication safety
• Quality improvement
• Optimizing medical regimens
• Patient education and adherence
Proposed Solutions

• Potential pharmacy policies
  – Contact PAH clinic or specialty pharmacy for:
    • Current dose, dosing weight, concentration, rate
  – Double-check all calculations
  – Obtain copy of titration schedule
  – Ensure pharmacy labels are clear
  – Ensure all relevant information is in medication administration record


Proposed Solutions

• Potential hospital/nursing policies
  – Develop formal prostacyclin administration policies
  – Provide ongoing staff education
  – Double-check cassette and rate changes regularly
  – Re-evaluate placement of back-up cassettes
  – Place markers near connection sites
    (“do not flush” or “dedicated line”)


A Model for Practice Change
Multidisciplinary Committee

- Identify stakeholders
  - Key physicians
  - Nursing
  - Pharmacy
  - Administrators
- Define current problems
- Delegate responsibilities

Prostacyclin Policies

- Interdisciplinary medication manual
- Key nursing resources
- Key pharmacy resources
- Readily accessible

Order Set Development

- Computerized physician order entry
- Required data elements
  - Route of administration
  - Correct formulation and vial concentration
  - Dosing weight
  - Dose
  - Final concentration
  - Base solution
  - Rate
  - Attending physician
Order Set Development

- Consider restricting by prescribing service/prescriber
- Location

Pharmacy Operations

New order: initiation vs. maintenance
When is first dose due?
Obtain patient-specific dosing chart
Double-check all calculations to verify current order
Compare with patient-specific dosing chart
Documentation: Create patient packet
(patient-specific dosing chart, order checklist, dispensing log)
Preparation and dispensing
Continuity of care

Pharmacy Operations

Prostacyclin flowchart
Checklist (treprostinil vs. epoprostenol)
Dispensing log (treprostinil vs. epoprostenol)
Continuity of care
Pharmacy Operations

- Streamline appropriate product selection and related supplies
- Meetings between specialty pharmacy supplier and hospital pharmacy team (clinical/operations/supply chain team)
- Centralize location
- Establish par levels
- Creation of product kits

Other Operational Pearls

- Use patient weight provided by specialty pharmacy vs. inpatient weight
- CADD® pumps vs. regular IV pumps
- Need for back-up cassettes (epoprostenol)

Education

- Mandatory monthly education with annual competency
  - Pharmacists & pharmacy technicians: pharmacotherapy, prostacyclin policies, order sets, pharmacy operations
  - Nursing: pathophysiology, hemodynamic monitoring, pharmacotherapy, equipment
Back to the Patient Case

CC/HPI: CJ is a 33-year-old female who presents to the PH clinic with c/o progressive dyspnea and fatigue x 3 weeks with 15 lbs. weight gain since last visit (3 months ago). Symptoms noted with minimal activities.

Initiate epoprostenol
• 2 ng/kg/min continuous IV infusion
• New order entered by heart failure fellow
• ICU pharmacist receives order

As the pharmacist in this case, what additional information would be important to know before proceeding?
Patient Case: Next Steps

- Contact physician that entered order and/or PAH clinical nurse
  - When is therapy to start?
  - Has IV CADD® pump been obtained?
- Locate “prostacyclin flowchart”
- Obtain documents for “patient packet”
  - “Patient-specific dosing chart”
    - Contact specialty pharmacy to determine dosing scheme
  - Veletri® “order checklist”
  - Veletri® “dispensing log”

Patient Case: Next Steps

- Verify dose and rate on “patient-specific dosing chart”

- Verify accuracy and completeness of inpatient order vs. “patient-specific dosing chart”
  - Vial amount, patient weight, rate, dose, final concentration, diluent
Patient Case: Final Steps

- Send Patient Packet to IV room pharmacist
- Notify IV room of time first dose is due
- IV room pharmacist serves as double-check
- Complete Veletri® “dispensing log”
- Maintain “patient packet” on file in pharmacy
- “Continuity-of-care” sheet
  - Note titration schedule (possible changes in cassette concentrations)

What additional opportunities exist for optimizing medications in this patient?
Please remember to complete and return the "Activity Evaluation"

Upcoming Educational Activity

Online Learning Activity
For healthcare professionals who were unable to participate in the presentation, an online learning activity based on the live program will be available.

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Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

**CE Value Statement:**

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

**REFLECT**

Consider my current knowledge and skills in managing PAH, and self-assess my professional development needs and goals.
PLAN

Develop a “Personal Learning Plan” to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.
List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.
Monitor progress regularly toward achievement of your goal.