

## VTE Prevention Across the Continuum: Applications of Clinical Evidence for Extended Prophylaxis from Inpatient to Outpatient Care



This session is supported by an educational grant from Portola Pharmaceuticals, Inc.

CELEBRATING  
10  
YEARS

## Faculty

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University of Utah Health Sciences Center

## Faculty Disclosures

**Dr. Munger** has disclosed no relevant financial relationships with any commercial interest.

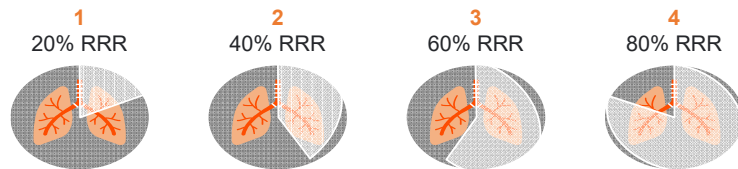
## Learning Objectives

- Quantify the clinical and economic burdens associated with VTE in patients admitted for acute medical illness as well as post-discharge
- Describe the standard of care for VTE prophylaxis in the acute hospitalization and post-discharge care settings
- Evaluate the latest clinical evidence associated with the use of DOACs for the acute and extended prophylaxis of VTE, particularly the implications of newly approved factor Xa inhibitors
- Incorporate risk stratification tools, patient-specific factors, and shared decision-making within the identification of patients who would most benefit from extended VTE prophylaxis
- Lead the interdisciplinary care team in the management of anticoagulant therapy for VTE prophylaxis, ensuring individualized therapeutic selection, patient-centric education and monitoring, and coordinated transitions of care from hospital to outpatient settings

VTE = venous thromboembolism; DOAC = direct oral anticoagulant.

Question: To what extent does pharmacologic prophylaxis reduce the risk of fatal VTE events in hospitalized medical patients?

### Audience Response Question



RRR = relative risk reduction.

## VTE in Medical Patients Is a Major Public Health Crisis

*"Deep vein thrombosis and pulmonary embolism represent a major public health problem, exacting a significant human and economic toll on the nation."*

— US Surgeon General (2008)



*"1 in 4 people worldwide dies of conditions caused by thrombosis. It is a leading cause of global death and disability."*

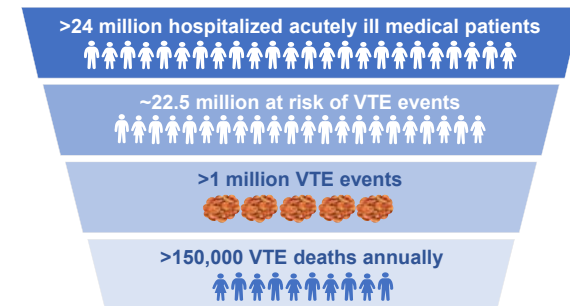
— World Thrombosis Day



Office of the Surgeon General; National Heart, Lung, and Blood Institute. 2008. *isth* [website]. Know thrombosis: learn & share. <http://www.worldthrombosisday.org/issue/thrombosis>. Accessed February 1, 2018. ISTH Steering Committee. Thrombosis: a major contributor to the global disease burden. October 9, 2014.

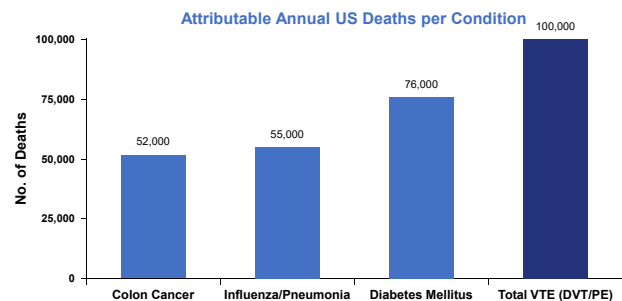
## Burden of Illness

In G7<sup>a</sup> countries, how big is the at-risk population of acutely ill medical patients annually?



<sup>a</sup>G7 countries: Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States. Cohen AT, et al. *N Engl J Med*. 2016;375:534-544. Roger VL, et al. *Circulation*. 2011;123:e18-e29. Ng TMH, et al. *Circ Heart Fail*. 2010;3(1):165-173. Kelly J, et al. *Stroke*. 2001;32(1):262-267. Tapson VF. *Proc Am Thorac Soc*. 2005;2(1):71-77.

## In the United States, Overall VTE Is Deadlier Than Colon Cancer, Diabetes Mellitus, Influenza, and Pneumonia

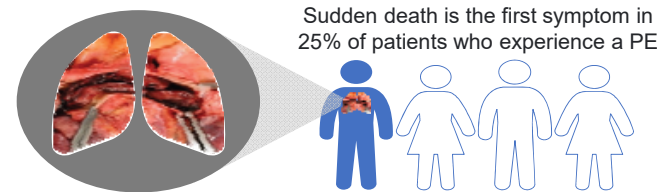


VTE causes ~100,000 confirmed annual deaths in the United States

DVT = deep vein thrombosis; PE = pulmonary embolism.  
 CDC. Colorectal (colon) cancer. <https://www.cdc.gov/cancer/colorectal/statistics>. Last updated January 23, 2018. Accessed February 1, 2018. CDC Health, United States, 2015. Office of the Surgeon General 2008.

## Up to 80% of Fatal VTE Events Occur in Acutely Ill Medical Patients

VTE can be a silent killer: Often the first symptom of a VTE is a fatal PE



Acutely ill medical patients have an 8x higher risk of VTE vs the general population

Huang W. *PLoS ONE*. 2015;10(3):e0121429. Futterman LG, et al. *Am J Crit Care*. 2004;13(5):431-436. Office of the Surgeon General and National Heart, Lung, and Blood Institute. *Call to Action to Prevent DVT and PE*. 2008. Beckman MG, et al. *Am J Prev Med*. 2010;38(4 suppl):S495-S501. Kahn SR, et al. *Chest*. 2012;141(2 suppl):e195S-e226S.

## Transitions of Care in VTE Research Program (University of Utah)

### • Department of Pharmacotherapy and Thrombosis Service Investigators

- Michael Feehan, PhD, Research Professor
- Dan Witt, PharmD, Vice Chair & Professor (Clinical)
- Ryan Fleming, PharmD, Manager, Thrombosis Service
- Mark Munger, PharmD, Professor & Associate Dean, College Affairs
- Stacy Johnson, MD, Medical Director, Thrombosis Service

### • 2-year program

- Initial qualitative interviews with patients
- National survey
- Pre- and post-evaluation of patients in Thrombosis Services

Feehan M, et al. *Patient VTE TOC Journey Model*. 2013:1-13.

## Background and Objectives

- VTE, including DVT of the lower and upper extremities and PE, is associated with reduced survival, a high rate of recurrence, poorer quality of life, and substantial healthcare costs
- Any interventions that can reduce the risk of VTE recurrence will benefit patients' personal lives, but also benefit society in terms of reduced healthcare costs

### Research Objectives

- Primary objective: To build a novel patient-centric statistical model of factors driving success and adversity in VTE care
- Model will ultimately be used to identify potential VTE care intervention targets and then validate the model by implementing targeted VTE care interventions in the University of Utah Health Care (UUHC) Thrombosis Services and measuring associated care outcomes

Feehan M, et al. *Patient VTE TOC Journey Model*. 2013:1-13.

## Quantitative Research Design: Patients

### • Online survey of 971 patients with VTE in the United States from May 10, 2016, through July 10, 2016

- Before entering the survey, patients were screened online based on the following criteria
  - Aged  $\geq 18$  years
  - Experienced at least one VTE event within the past 2 years
  - Not diagnosed with cancer within the past 2 years
- Quotas for patients with VTE were set to allow adequate representation within subgroups of interest

### • Report based on data from 907 patients after the data set was “cleaned” to remove erroneous responses

Feehan M, et al. *Patient VTE TOC Journey Model*. 2013:1-13.

## Transitions of Care in VTE Research Program (University of Utah)

Patient Characteristics	
Age (years)	52.4 $\pm$ 14.4
Gender (M:F %)	M:F 43:57
Race	White: 89% / Black: 7% Asian: 2% / Other: 2%
Comorbidity Index	3.32 $\pm$ 2.78
Previous Patient Diagnoses	Anxiety
	27%
	Asthma/COPD
	16% / 13%
	Depression
DVT/PE/Both	28%
	Heart Disease
	27%
	Hypertension
# of DVT Episodes/Lifetime	46%
	Hypercholesterolemia
	38%
64% / 18% / 18%	
# of DVT Episodes/Lifetime	1
	35%
	2
2+	24%
	65%

COPD = chronic obstructive pulmonary disease.  
Feehan M, et al. *Patient VTE TOC Journey Model*. 2013:1-13.

## High Emotional Impact of VTE

- Extracted themes from 17 qualitative online interviews with patients with VTE across the country in March 2016
- Patient stories highlighted the **emotional impact of VTE** at all stages of the journey from diagnosis to maintenance therapy, and from hospital to home
- Dangerous animals typified life with VTE



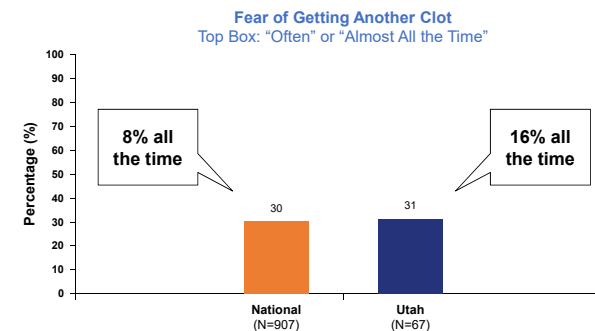
“I was **terrified**. I had almost died the day before; it was **deeply traumatic**”

“I have **sought help for stress management**, adjustment due to health changes and **depression**”



Feehan M, et al. Emotional Impact of Venous Thromboembolism (VTE): A Qualitative Study of Patients' Journeys. *Inside Patient Care*. 2017;5:3.

## Patients Fear Future Clots

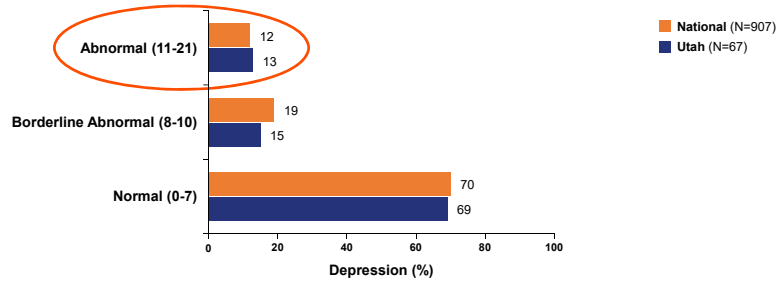


Feehan M, et al. Emotional Impact of Venous Thromboembolism (VTE): A Qualitative Study of Patients' Journeys. *Inside Patient Care*. 2017;5:3.



## More Than 10% Are Currently Depressed

Hospital Anxiety and Depression Scale (HADS)



Feehan M, et al. Emotional Impact of Venous Thromboembolism (VTE): A Qualitative Study of Patients' Journeys. *Inside Patient Care*. 2017;5:3.

## Emotional Harms Associated with Multiple Factors

- Provisional modeling of the national data showed **emotional harms** (ie, a composite measure of anxiety, depression, emotional distress, or cognitive impairment) were significantly associated ( $P<.05$ ) with:
  - High fear of another clot
  - Poor health literacy
  - Having multiple physical comorbidities
  - Being non-white
  - Younger age
  - Poor health locus of control – Lack of perceived self-control over health
  - Having had a physician make mistakes in the care of VTE
  - Barriers to care (eg, difficulty in paying for healthcare, paying for VTE medications, transportation issues, needing the support of others to obtain care)

Waldron B. Clot Connect [website]. Last updated February 28, 2012. Accessed February 5, 2018.

## VTE Has a Substantial Economic Impact<sup>a</sup>

<b>Total VTE medical costs</b>	<b>\$6.7-\$9.8 BILLION per year</b>
<b>Direct medical costs for acute treatment</b>	\$11,500-\$14,900 per adult patient in 1st year
<b>Costs of VTE treatment and related complications</b>	\$17,900-\$23,100 per adult patient >1 year <sup>b</sup>

<sup>a</sup>Costs reported in 2014 US dollars (rounded to the nearest \$100) based on an incidence-based estimate of 3 published studies. Total annual medical costs based on an estimated 375,000-425,000 newly diagnosed cases per year.

<sup>b</sup>Includes (after the first year) post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, recurrent VTE, anticoagulation-related adverse drug events. Grosse SD, et al. *Thromb Res*. 2016;137:3-10.

## At-Risk Patients

## Most Hospitalized Patients Are Non-Surgical Medical Patients

In a multi-national, cross-sectional study of 68,183 hospital patients

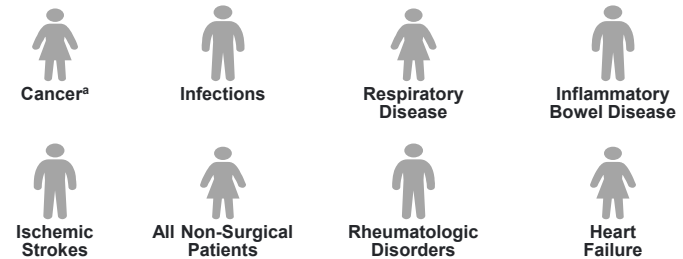


Nearly half of all hospitalized medical patients are at risk of VTE

Cohen AT, et al. *Lancet*. 2008;371(9610):387-394.

## Who Are Acutely Ill Medical Patients?

IMMOBILITY • HYPERCOAGULABILITY • INFLAMMATION



<sup>a</sup>Cancer requiring primary therapy or therapy for complications.  
Di Nisio M, et al. *Drug Des Devel Ther*. 2013;7:973-980.

## For Acutely Ill Medical Patients, Immobilization<sup>a</sup> Extends VTE Risk after Discharge

- Immobilization can continue for weeks after hospitalization regardless of post-discharge setting

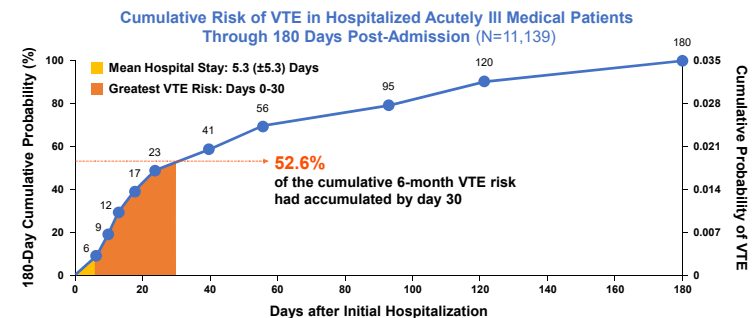


- Shorter hospital stays lengthen periods of outpatient bed-rest and immobility
- Acute medical illness flare-ups or exacerbations can require re-hospitalization and further immobilization

<sup>a</sup>In clinical studies, immobilization is defined as confinement to bed or to a chair at bedside.

Cohen AT, et al. *N Engl J Med*. 534-544. Rocha AT, et al. *Vasc Health Risk Manage*. 2007;3(4):533-553. Robinson AM. *Ann Longterm Care*. 2013;21(9):28-32. Spencer FA, et al. *Arch Intern Med*. 2007;167(14):1471-1475. Björk E, et al. *J Thromb Haemost*. 2016;14(12):2368-2375.

## In Hospitalized, Acutely Ill Medical Patients, More Than Half of VTE Events Occur Within 30 Days

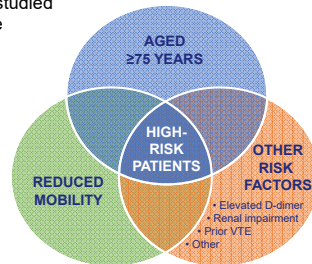


More than half of the cumulative VTE risk occurs within 30 days

Amin AN, et al. *J Hosp Med*. 2012;7(3):231-238.

## Effective Extended-Duration VTE Prophylaxis Is Needed for Acutely Ill Medical Patients at High Risk

- Enoxaparin, rivaroxaban, and apixaban were studied as extended-duration VTE prophylaxis in three phase 3 trials
- These trials included patients with common risk factors
  - Aged  $\geq 75$  years
  - Reduced mobility
  - Elevated D-dimer
  - Renal impairment
  - Prior VTE
  - Other

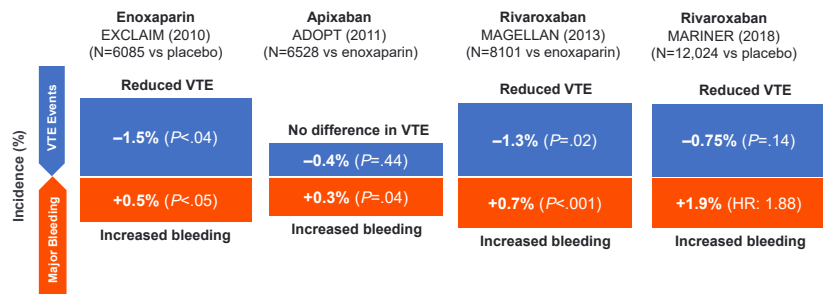


7.7 million US patients at risk of VTE

Cohen AT, et al. *J Thromb Haemost.* 2014;14:473-493. Goldhaber SZ, et al. *N Engl J Med.* 1998;339:93-104. Hull RD. *Ann Intern Med.* 2010;153(1):8-18. Anderson FA, et al. *Am J Hematol.* 2007;82:777-782.

Unmet Need

## For Acutely Ill Medical Patients, No Anticoagulant Is Approved for VTE Prevention in the Extended-Duration Setting



No agent demonstrated a compelling net clinical benefit

Hull RD, et al. *Ann Intern Med.* 2010;153(1):8-18. Goldhaber SZ, et al. *N Engl J Med.* 2011;365(23):2167-2177. Cohen AT, et al. *N Engl J Med.* 2013;368(6):513-523. Spyropoulos AC, et al. *N Engl J Med.* August 26, 2018. doi: 10.1056/NEJMoa1805090.

## For At-Risk, Hospitalized, Acutely Ill Medical Patients, Guidelines Recommend Only Initial VTE Prophylaxis

### • All major clinical guidelines weigh VTE risk against risk of serious bleeding with treatment

- Guidelines recommend an initial short-duration course of pharmacologic prophylaxis (ie, 6-14 days) for acutely ill medical patients with high VTE risk and low bleeding risk
  - Current recommended options in the United States include low-molecular-weight heparin, unfractionated heparin, or fondaparinux
- Recommendations are informed by the high rate of VTE events and trial data showing a net clinical benefit with in-hospital prophylaxis

Guidelines do not recommend extended-duration prophylaxis for acutely ill medical patients because clinical trials have failed to identify a safe post-discharge therapy

Kahn S, et al. *Chest.* 2012;141(2 suppl):e195S-e226S. Korjian S, et al. *J Cardiovasc Pharmacol Ther.* 2016;21(3):227-232.

## Meeting the Need? You Decide

### APEX Trial

## APEX Trial

### OBJECTIVE

### PATIENTS

### STUDY DESIGN

### ENDPOINTS

To demonstrate the safety and efficacy of in-hospital and extended-duration (35-42 days) anticoagulation with betrixaban compared with standard-of-care anticoagulation with enoxaparin (6-14 days) followed by placebo for prevention of VTE in acutely ill medical patients

Cohen AT, et al. *Am Heart J*. 2014;167(3):335-341.

## New Oral Anticoagulants (Factor Xa Inhibitors): Pharmacodynamics and Pharmacokinetics

Property	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism of Action	Direct IIa Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor	Direct Xa Inhibitor
Bioavailability	6%-7%	80%	50%	62%	34%
T <sub>max</sub>	1.5 hours	2-4 hours	2-3 hours	1-2 hours	3-4 hours
T <sub>1/2</sub>	12-14 hours	9-13 hours	8-15 hours	8-11 hours	19-27 hours
Hepatic Metabolism	No	Yes	Yes	Yes	No
Drug Interactions	P-gp	CYP3A4	CYP3A4	P-gp	P-gp
Protein Binding	35%	90%	87%	55%	60%
Dialyzable	Yes	No	No	No	No
Measurement	ECT, TT, aPTT	Anti-Xa, PT	Anti-Xa, dPT	Anti-Xa, PT	Anti-Xa, PT
Renal Elimination	80%	35%	25%	40%	11%
Renal Dosing	Yes	Yes	No?	Yes	Yes
Antidote	No	No	No	No	No

FDA [website]. Drugs@FDA approved drug products.  
<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208383>. Accessed February 1, 2018.

## Comparison of Agents

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Betrixaban
Special Instructions	None	Do not chew, break open capsules - ↑ bioavailability by 75% Keep in original bottle and tightly capped Must use within 4 months of opening	None	None	None
Pre-Procedure Dosing	Stop 5-6 days prior procedure May need bridging	Skip 2-8 doses depending on procedure and renal function No need for bridging	Stop >24 hours before OR and other interventions	Stop 24-48 hours before elective OR and other interventions	Stop 72 hours before elective OR and other interventions
Diet Considerations	Consistent intake of Vitamin K-containing foods	None	Take with food	None	Take with food at same time each day
Cost	\$4/month + \$20/INR (Annual cost ≈\$1000)	\$200-400/month Patient Assistance Program (Annual cost ≈\$2400-\$4800)	\$299/month (AWP) CarePath™ Patient Support and Assistance Program (Annual cost ≈\$3600)	\$299/month (AWP) Eliquis® 360 Support Patient Support and Assistance Program (Annual cost ≈\$3600)	\$15/40 or 80 mg (AWP) CoverMyMeds™ Program Patient Support and co-pay offset cards (42-day cost ≈\$610)

Note: Betrixaban is only used for 42 days; therefore, annual cost is not appropriate from the cost basis.

INR = international normalized ratio; AWP = average wholesale price.

FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208383>. Accessed February 1, 2018.

## APEX Trial Inclusion Criteria

### OBJECTIVE

### PATIENTS INCLUDED

### STUDY DESIGN

### ENDPOINTS

#### HOSPITALIZED FOR ACUTE MEDICAL ILLNESS

**Heart Failure, Respiratory Failure, Infectious Disease, Rheumatic Disease, or Ischemic Stroke**

#### EXPECTED MODERATE / SEVERE IMMOBILITY

Age and Additional Risk Factors			
≥75 Years	60 to 74 Years	40 to 59 Years	Additional Risk Factors
Eligible	2 additional risk factors OR D-dimer ≥2x ULN	History of VTE OR History of cancer +	<ul style="list-style-type: none"> <li>Previous VTE or superficial vein thrombosis</li> <li>History of NYHA class III or IV HF</li> <li>Concomitant acute infection</li> <li>Obesity (BMI &gt;35)</li> <li>History of cancer</li> <li>Inherited or acquired thrombophilia</li> <li>Current use of erythropoiesis-stimulating agent</li> <li>Hormone therapy</li> </ul>
		1 additional risk factor OR D-dimer ≥2x ULN	

ULN = upper limit of normal; NYHA = New York Heart Association; HF = heart failure; BMI = body-mass index.  
Cohen AT, et al. *Am Heart J.* 2014;167(3):335-341.

## APEX Trial Exclusion Criteria

### OBJECTIVE

### PATIENTS EXCLUDED

### STUDY DESIGN

### ENDPOINTS

- End-stage renal disease with CrCl <15 mL/min, or requiring dialysis
  - APEX is the first extended thromboprophylaxis trial to enroll patients with CrCl <30 mL/min
- Anticipated need for prolonged anticoagulation
- Current intake of dual antiplatelet therapy
- Anticipated major surgery
- History of clinically significant bleeding within 6 months prior to enrollment
- History of intracranial bleeding, head trauma, or known intracranial lesions
- History of significant gastrointestinal, pulmonary, or genitourinary bleeding, ongoing chronic peptic ulcer disease, or ongoing or acute gastritis within 2 years prior to enrollment
- Hemoglobin <9.5 g/dL or unstable/declining hemoglobin

CrCl = creatinine clearance.  
Cohen AT, et al. *N Engl J Med.* 2016;375(6):534-544. Cohen AT, et al. *Am Heart J.* 2014;167(3):335-341.

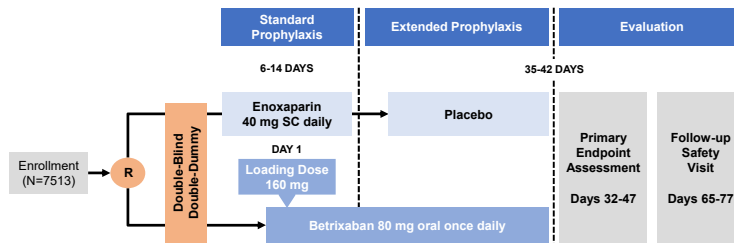
## APEX Trial

### OBJECTIVE

### PATIENTS

### STUDY DESIGN

### ENDPOINTS



P-gp = P-glycoprotein; SC = subcutaneous.  
FDA (website). Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208383>.  
Accessed February 1, 2018. Cohen AT, et al. *Am Heart J.* 2014;167(3):335-341. Cohen AT, et al. *N Engl J Med.* 2016;375(6):534-544.

## APEX Trial (cont)

### OBJECTIVE

### PATIENTS

### STUDY DESIGN

### ENDPOINTS

#### Primary Efficacy Endpoint

- Composite of VTE-related death, non-fatal PE, asymptomatic proximal DVT, or symptomatic DVT

#### Secondary Efficacy Endpoint

- Composite of symptomatic VTE (VTE-related death, non-fatal PE, or symptomatic DVT) through day 42

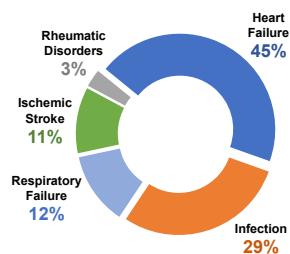
#### Primary Safety Endpoint

- Occurrence of major bleeding through 7 days after discontinuation of all study medication

Cohen AT, et al. *Am Heart J.* 2014;167(3):335-341.

## APEX Patient Characteristics at Baseline

### Primary Acute Medical Illness



### Additional VTE Risk Factors

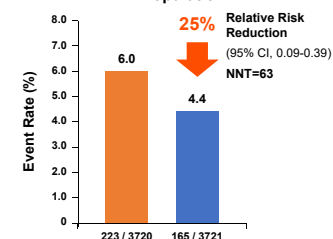
	% of Patients
Aged ≥75 years	68
D-dimer ≥2x ULN	62
History of NYHA class III or IV heart failure	23
Obesity (BMI >35)	19
Severe varicosities	19
Concurrent acute infection	16
History of cancer	12
Previous VTE	8
Hormone replacement therapy	1.0
Inherited or acquired thrombophilia	0.1

FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daif/index.cfm?event=overview.process&appno=208383>. Accessed February 1, 2018. Cohen AT, et al. *N Engl J Med*. 2016;375(6):534-544.

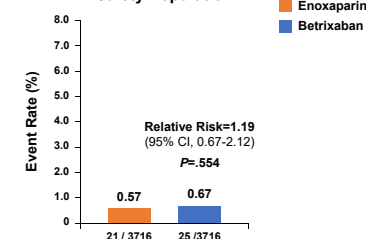
## Primary Efficacy and Safety Endpoint

### 80-mg & 40-mg doses

#### PRIMARY EFFICACY OUTCOME Total VTE or VTE-Related Death mITT Population



#### PRIMARY SAFETY OUTCOME Major Bleeding Safety Population

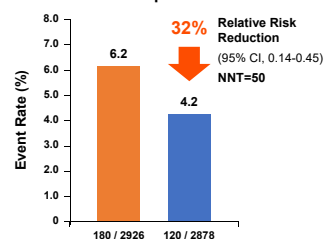


mITT = modified intent to treat; NNT = number needed to treat.  
FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daif/index.cfm?event=overview.process&appno=208383>. Accessed February 1, 2018. Cohen AT, et al. *N Engl J Med*. 2016;375(6):534-544.

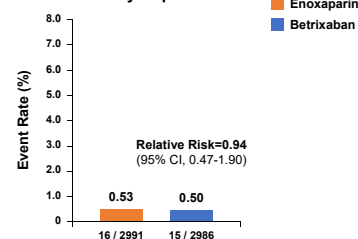
## Primary Efficacy and Safety Endpoint (cont)

### 80-mg dose

#### PRIMARY EFFICACY OUTCOME Total VTE or VTE-Related Death mITT Population



#### PRIMARY SAFETY OUTCOME Major Bleeding Safety Population

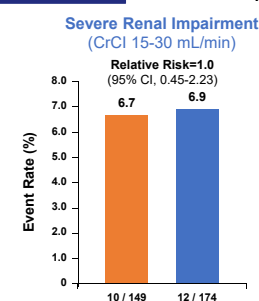


FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daif/index.cfm?event=overview.process&appno=208383>. Accessed February 1, 2018. Cohen AT, et al. *N Engl J Med*. 2016;375(6):534-544.

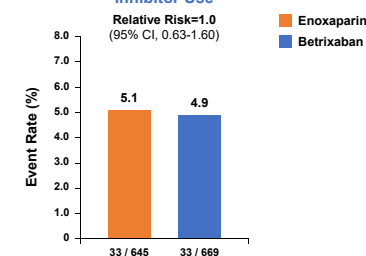
## Primary Efficacy Endpoint

### 40-mg dose

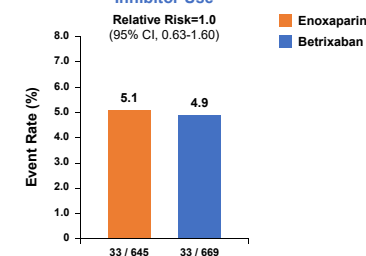
#### Total VTE or VTE-Related Death mITT Population



#### Severe Renal Impairment (CrCl 15-30 mL/min)

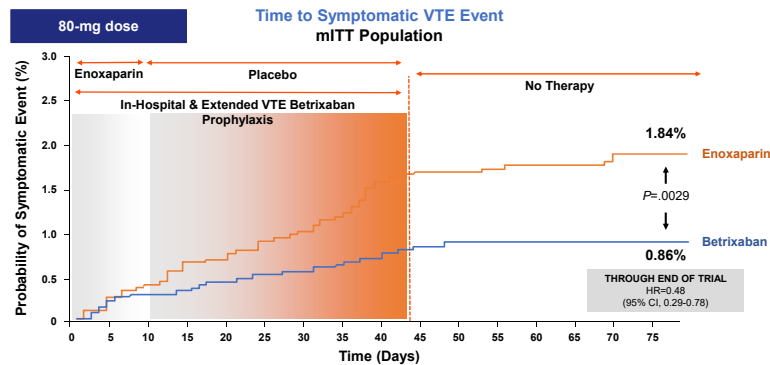


#### Concomitant P-gp Inhibitor Use



FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daif/index.cfm?event=overview.process&appno=208383>. Accessed February 1, 2018. Cohen AT, et al. *N Engl J Med*. 2016;375(6):534-544.

## Time to Symptomatic VTE Event Through End of Trial (Post Hoc)

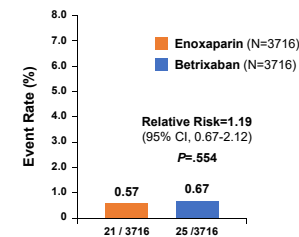


Gibson CM, et al. Modified poster presented at Isth SSC 2016; May 25-28, 2016; Montpellier, France.

## Primary Safety Endpoint

**80-mg & 40-mg doses**

**PRIMARY SAFETY OUTCOME  
Major Bleeding  
Safety Population**



**PRIMARY SAFETY OUTCOME  
Types of Major Bleeding  
Safety Population**

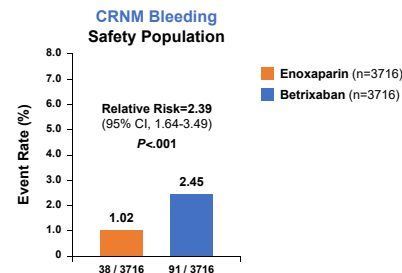
	Enoxaparin (N=3716) n (%)	Betrixaban (N=3716) n (%)
Gastrointestinal	9 (0.24)	19 (0.51)
Intracranial hemorrhage	7 (0.19)	2 (0.05)
Intraocular	1 (0.03)	0 (0)
Fatal bleeding	1 (0.03)	1 (0.03)

FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208383>. Accessed February 1, 2018. Cohen AT, et al. *N Engl J Med*. 2016;375(6):534-544.

## Secondary Safety Endpoint: CRNM Bleeding

**80-mg & 40-mg doses**

- Most CRNM bleeding events were mild to moderate in severity and did not require or prolong hospitalization
  - CRNM is defined as overt bleeding not meeting criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, cessation of study treatment, or with discomfort for the patient



CRNM = clinically relevant non-major.  
FDA [website]. Drugs@FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208383>. Accessed February 1, 2018.

## Risk Stratification Tools, Patient-Specific Factors, and Shared Decision-Making

- Objective 4:** Incorporate risk stratification tools, patient-specific factors, and shared decision-making within the identification of patients who would most benefit from extended VTE prophylaxis
- Risk Stratification Tools and Patient-Specific Factors**
  - Padua Prediction Score for Risk of VTE (<https://www.mdcalc.com/padua-prediction-score-risk-vte>)
  - International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE Risk Assessment; [http://www.outcomes-umassmed.org/improve/risk\\_score/index.html](http://www.outcomes-umassmed.org/improve/risk_score/index.html))
- Shared Decision-Making/Team-Based Care**
  - An Interdisciplinary Approach to Preventing VTE (<https://scholarsphere.psu.edu/downloads/6t148fg135>)

## Patient Case: 76-Year-Old Man with Heart Failure<sup>a</sup>



<sup>a</sup>This is a hypothetical patient case.

## Patient Case: 76-Year-Old Man with Heart Failure (cont)

### Initial presentation

- A 76-year-old man is admitted to the **ED** with persistent cough, dyspnea, and bilateral edema in the legs and is diagnosed with an acute heart failure exacerbation
- He has difficulty moving about and was brought **to the ED** by his wife, who says that because of his breathing difficulty, he **was experiencing restricted mobility** and was unable to get out of bed for the past 3 days, unless absolutely necessary

### Medical history

- CHF (NYHA class III), LVEF 29%
- Hypertension
- BPH
- GERD

### Current medications

- Lisinopril
- Furosemide
- Tamsulosin
- Esomeprazole

### Allergies

- Penicillin

### Social history

- Retired teacher who lives with his wife, who is his primary caretaker

ED = emergency department; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; BPH = benign prostatic hyperplasia; GERD = gastroesophageal reflux disease.

## Patient Case: 76-Year-Old Man with Heart Failure (cont)

Height	Weight	BMI
5'7"	72.5 kg	25.1 kg/m <sup>2</sup>

### Pertinent physical examination findings

- Neck:** Jugular venous distension
- Chest:** Lungs are dull to percussion with bilateral crackles; x-ray shows bilateral pleural effusions and cardiomegaly
- Heart:** S3 gallop noted, RRR, no fibrillation or flutter
- Extremities:** Bilateral lower extremity edema, minimal clubbing
- Abdomen:** Liver edge palpable and tender, consistent with hepatomegaly

### Vitals

- HR: 112 bpm
- BP: 150/90 mm Hg
- RR: 24
- Temp: 99° F
- O<sub>2</sub> saturation: 91%

### BMP

Na	Cl	BUN
133	93	33
K	HCO <sub>3</sub>	Cr
3.9	23	1.6

### CrCl

40 mL/min  
(Cockcroft-Gault using actual body weight)

### CBC

- WBC: 6300 cells/mcL (normal differential)
- Hgb/Hct: 15.6 g/dL /44%
- Platelets: 230,000/m<sup>3</sup>

### Urinalysis

Normal

### LFTs

Normal

### Other

Normal PT and INR

BMI = body mass index; BMP = basic metabolic panel; BP = blood pressure; bpm = beats per minute; BUN = blood urea nitrogen; CBC = complete blood count; Hgb = hemoglobin; Hct = hematocrit; HR = heart rate; INR = international normalized ratio; LFT = liver function test; PT = prothrombin time; RR = respiratory rate; RRR = regular rate and rhythm; Temp = temperature; WBC = white blood cells.

## Patient Case: 76-Year-Old Man with Heart Failure (cont)

### Assessment of VTE risk

- Risk factors for VTE in this patient include:
- Limited mobility (bedridden for 3 days and anticipated length of hospitalization at least 4 days)
  - Hospitalization for heart failure (candidate for admission)
  - 76 years old

### APEX criteria met

- Aged ≥40 years
- Hospitalization for acute medical illness (heart failure)
- Moderate to severe immobilization at least 24 hours and expected hospitalization at least 3 days

### PADUA prediction score

Risk Factor	Points
Heart failure	1
Elderly (≥70 years)	1
Immobilization for ≥3 days	3
<b>Total score</b>	<b>5</b>
Scores ≥4 associated with high VTE risk	

### Improve VTE risk assessment

Risk Factor	Points
Aged >60 years	1
Immobilization for at least 7 days (prior to and during hospital admission)	1
<b>Total score</b>	<b>2</b>
Scores ≥2 associated with high VTE risk	



## Patient Case: 76-Year-Old Man with Heart Failure (cont)

### Patient management Audience Response Question

- Patient requires **observation in the ED for 48 hours** for decompensated CHF, later transferred to the general medical floor, and hospitalized for a total of 7 days
- During his **hospitalization**, the patient receives supplemental oxygen to manage hypoxemia and IV diuretics for volume overload
- He is a candidate for extended VTE prophylaxis
- QUESTION: Which of the following medications should he receive?
  - A. Enoxaparin
  - B. Apixaban
  - C. Betrixiban
  - D. Rivaroxaban

IV = intravenous.

49

## Coordinated Transitions of Care

- **Objective 5:** Lead the interdisciplinary care team in the management of anticoagulant therapy for VTE prophylaxis, ensuring individualized therapeutic selection, patient-centric education and monitoring, and coordinated transitions of care from hospital to outpatient settings

### Transitions of Care

Successful transitions of care require:

1. Complete and accurate exchange of information
2. Care management, medication continuity, laboratory monitoring
3. Communication between healthcare professionals and the patient and caregivers (often the weak link)
4. Pharmacists can play a central role in transitions of care
  - Jackson Memorial Hospital (Miami) DVT Program
  - Patient Education, Treatment, and Patient Selection
  - Reduced LOS, ED Visit Time Reduced

Owens GM, et al. *Am J Manag Care.* 2014;20:S81-S91. Lenchus JD. *Adv Ther.* 2016;33:29-45.

## Summary

- In medically ill patients, **60% of VTE risk accumulates from admission to 40 days**
- Betrixaban is the **only current oral anticoagulant indicated** for prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other VTE risk factors
- Betrixaban 80 mg demonstrated a **32% relative risk reduction** in VTE and VTE-related death vs enoxaparin (NNT=50)
- Will all DOACs use caution in conditions where an **increased risk of bleeding** exists or is suspected?
  - All DOACs increase the risk of bleeding and can cause serious and potentially fatal bleeding
  - Caution may occur in patients undergoing neuroaxial anesthesia or spinal puncture—long-term permanent paralysis
  - Caution with drugs affecting hemostasis: Aspirin, antiplatelet drugs, other anticoagulants, heparin, selective serotonin reuptake inhibitors, and nonsteroidal anti-inflammatory drugs
  - We remain without an active reversal agent for factor X DOACs

Questions?

## Additional Slides for Q/A Only

### Phase 3: Acknowledge Risk of Emotional Harm

- Updated 'welcome letter' and external webpage

- "...people who have a blood clot can feel anxious or depressed. If you or a family member are worried about your behavior or feelings, please let us know, so we can offer help."
- Online resources/patient support groups added

- Reference card with open-ended questions (target first 30 days post-VTE)

- What questions do you have about our educational materials or online resources?
- What concerns have you had about bleeding?
- What concerns have you had about having another clot?
- How has your recent clot affected you emotionally?

Document  
positive findings

### Phase 3: Responding to Emotional Harm

- How should you respond to patients who are experiencing emotional harms?

- "These feelings are not uncommon, and we do have resources available to help. Would you like me to explain the resources we have that could help?"
- PULSE – "Patient Resources" page

#### Emotional Distress Support

1. May refer to PCP or Thrombosis MD
2. Offer Online Support Groups
  - a. [North American Thrombosis Forum](#)
  - b. [National Blood Clot Alliance](#)
3. Refer to Social Workers in Community Clinics
4. [Crisis Intervention & Hospital Diversion Services](#)

Document if any  
of these are offered

# Addressing Diagnostic and Therapeutic Challenges in Pulmonary Arterial Hypertension through Pharmacist Intervention



This session is supported by an educational grant from Actelion Pharmaceuticals US, Inc.

CELEBRATING  
10  
YEARS

## Faculty

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New York Presbyterian Hospital

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## Disclosures

**Dr. Jennings:** Has nothing to disclose in relation to this presentation

This continuing medical education activity includes device brand names for participant clarity purposes only, due to the presence of different branded versions of the same device. No product promotion or recommendation should be inferred.

## Learning Objectives

- Recognize the barriers to a timely PAH diagnosis and the clinical and socioeconomic impact of diagnostic delays
- Outline the diversity of PAH pathophysiologic mechanisms, therapeutic targets, and patient types with respect to impact on clinical outcomes and therapeutic design
- Evaluate traditional and newer approaches to the management of PAH with respect to their mechanisms of action, efficacy, safety, indications, and appropriate use across patient populations
- Employ pharmacy practice strategies to optimize the long-term management of PAH through informed, individualized, and coordinated care

PAH = pulmonary arterial hypertension.

## Patient Case

- HL is a 43-year-old mother of three who presented with a 2-month history of dyspnea on exertion and fatigue consistent with class II to class III symptoms
- She reports a 1-year use of phentermine for weight loss prior to symptom onset
- She also reports that her mother had PAH and died at the age of 47 years
- She was diagnosed with PAH (heritable vs drug-induced) based on RHC

RHC = right heart catheterization.

## Definition of PH vs PAH

Right Heart Catheterization Confirmed		Diagnosis
Increased mPAP	≥25 mm Hg	PH
Increased mPAP AND Normal PCWP	≥25 mm Hg AND <15 mm Hg	PAH

mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension. Simonneau G, et al. *J Am Coll Cardiol*. 2013;62:D34-D41.

## Clinical Classification

<b>1. PAH</b> <ul style="list-style-type: none"> <li>• Idiopathic PAH</li> <li>• Heritable</li> <li>• Drug and toxin-induced</li> <li>• Associated with:               <ul style="list-style-type: none"> <li>- Connective tissue disorders</li> <li>- Human immunodeficiency virus infection</li> <li>- Portal hypertension</li> <li>- Congenital heart disease</li> <li>- Schistosomiasis</li> </ul> </li> </ul>	<b>3. PH Owing to Lung Diseases and/or Hypoxia</b> <ul style="list-style-type: none"> <li>• Chronic obstructive pulmonary disease</li> <li>• Interstitial lung disease</li> <li>• Other pulmonary diseases with mixed restrictive and obstructive pattern</li> <li>• Sleep-disordered breathing</li> <li>• Alveolar hypoventilation disorders</li> <li>• Chronic exposure to high altitude</li> <li>• Developmental abnormalities</li> </ul>
<b>1'. Pulmonary Veno-Occlusive Disease (PVOD)</b>	<b>4. Chronic Thromboembolic PH (CTEPH)</b>
<b>1". Persistent PH of Newborn</b>	<b>5. PH with Unclear Multifactorial Mechanisms</b> <ul style="list-style-type: none"> <li>• Hematologic disorders (including chronic hemolytic anemia)</li> <li>• Systemic disorders</li> <li>• Metabolic disorders</li> <li>• Others</li> </ul>
<b>2. PH Owing to Left Heart Disease</b> <ul style="list-style-type: none"> <li>• Left ventricular systolic dysfunction</li> <li>• Left ventricular diastolic dysfunction</li> <li>• Valvular disease</li> <li>• Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</li> </ul>	

Simonneau G, et al. *J Am Coll Cardiol*. 2013;62:D34-D41.

## Drug- and Toxin-Induced PAH

Definite	Possible
<ul style="list-style-type: none"> <li>• Aminorex</li> <li>• Fenfluramine</li> <li>• Dexfenfluramine</li> <li>• Toxic rapeseed oil</li> <li>• Benfluorex</li> <li>• SSRIs</li> </ul>	<ul style="list-style-type: none"> <li>• Cocaine</li> <li>• Phenylpropanolamine</li> <li>• St. John's wort</li> <li>• Chemotherapeutic agents</li> <li>• Interferon-α or -β</li> <li>• Amphetamine-like drugs</li> </ul>
Likely	Unlikely
<ul style="list-style-type: none"> <li>• Amphetamines</li> <li>• L-Tryptophan</li> <li>• Methamphetamines</li> <li>• Dasatinib</li> </ul>	<ul style="list-style-type: none"> <li>• Oral contraceptives</li> <li>• Estrogen</li> <li>• Cigarette smoking</li> </ul>

SSRI = selective serotonin reuptake inhibitor. Simonneau G, et al. *J Am Coll Cardiol*. 2013;62:D34-D41.

## Epidemiology

- WHO group 1
- Incidence: 15 per million people
- Demographics
  - Mean age, 50 ± 14 years
  - 80% female
- 56% have symptoms with minimal activity or at rest
- Delay from symptom onset to diagnosis: 27 months

WHO = World Health Organization.  
McGoan MD, et al. *J Am Coll Cardiol*. 2013;62:D51-59. McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

## Functional Classification

### WHO

- **Class I:** Symptoms elicited at levels of exertion that would limit normal individuals
- **Class II:** Symptoms on ordinary exertion
- **Class III:** Symptoms on less-than-ordinary exertion
- **Class IV:** Symptoms at rest

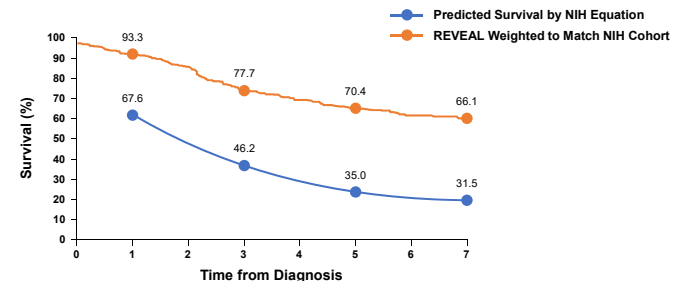
Pulmonaryfunctionrn.com. Functional classification of pulmonary hypertension. Four functional classes of pulmonary hypertension. <http://pulmonaryhypertensionrn.com/functional-classification-of-pulmonary-arterial-hypertension-pah/>. Accessed February 23, 2017.  
Mathier MA. Medscape Education. 2006;10:2. <http://www.medscape.org/viewarticle/544175>. Accessed February 23, 2017.

## Clinical Presentation

Common Initial Symptom	Patients (%)
Dyspnea	60
Fatigue	19
Syncope	13
Chest pain	7
Palpitations	5
Leg edema	3

McGoan M, et al. *Chest*. 2004;126:14S-34S.

## REVEAL Registry: Survival



No. at Risk:  
Matched REVEAL 279 377 390 388 328 240 153 88

REVEAL = Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management; NIH = National Institutes of Health.  
Benza RL, et al. *Chest*. 2012;142:448-456.

## Risk Assessment

### • Low risk

- No RV failure
- Gradual symptom progression
- WHO FC II, III
- Peak  $\text{VO}_2 > 10.4 \text{ mL/min/kg}$
- Minimal BNP elevation
- Preserved cardiac index

### • High risk

- Evidence of RV failure
- Rapid symptom progression
- WHO FC IV
- Peak  $\text{VO}_2 < 10.4 \text{ mL/min/kg}$
- Significant BNP elevation
- Low cardiac index

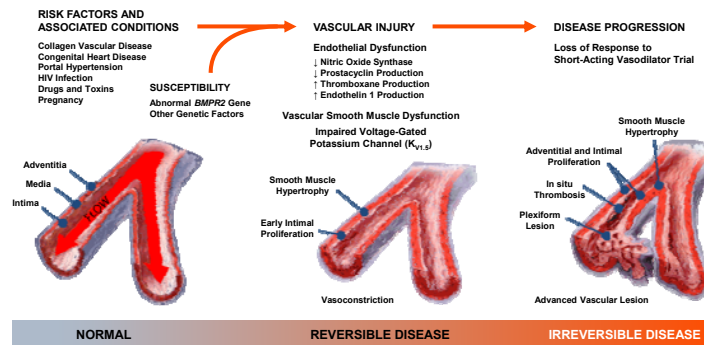
RV = right ventricular; BNP = brain natriuretic peptide; FC = functional classification.  
McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

## Hospitalizations and Costs

- Hospitalization for worsening PAH
  - Associated with poor prognosis
  - Costly
- Hospitalization costs greatly exceed pharmacy costs
  - Average costs of initial PAH-related hospitalization nearly \$40,000
  - Post-initial hospitalization, subsequent admissions result in longer, more expensive stays
- Total healthcare costs: ~\$8000 per-patient-per-month

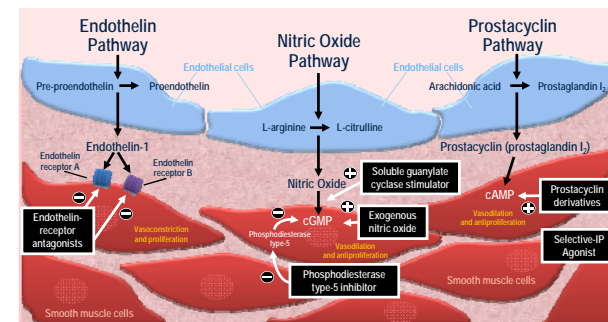
Campo A, et al. *Eur Respir J*. 2011;38:359-367. Sikirica M, et al. *BMC Health Services Research*. 2014;14:676. Burke JP, et al. *Am J Managed Care*. 2015;21:S47-S58. Galie N, et al. *J Am Coll Cardiol*. 2013;62:D60-D72.

## Pathogenesis



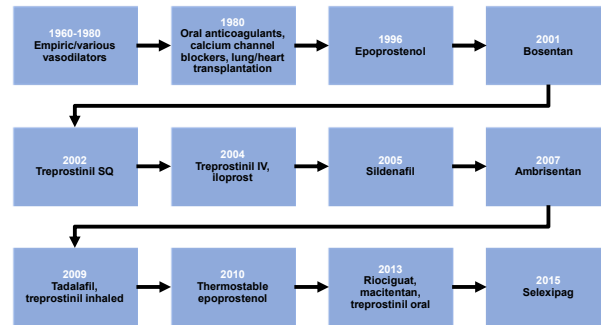
Galie N. *JAMA*. 2000;284(24):3160-3168.

## Therapeutic Targets



cGMP = cyclic guanosine monophosphate; cAMP = cyclic adenosine monophosphate.  
Humbert M, et al. *N Engl J Med*. 2004;351:1425-1436.

## Pharmacotherapy Timeline



SQ = subcutaneous; IV = intravenous.

## Treatment Goals

- WHO FC I or II
- 6-minute walk distance  $\geq 380$  m to 440 m
- Normalization of RV function
- Normalization of biomarkers
- Prevention of hospitalization or clinical deterioration
- Peak oxygen consumption of  $>15$  mL/min/kg

McLaughlin VV, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D73-D81.

## Treatment Failures

Component	Definition
Hospitalization for worsening PAH	Any hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid therapy
Disease progression	A decrease of $>15\%$ from baseline in the 6-minute walk distance combined with WHO FC III or IV symptoms
Unsatisfactory long-term clinical response	Any decrease from baseline in 6-minute walk distance and WHO FC III symptoms assessed

Gallè N, et al. *N Engl J Med*. 2015;373:834-844.

## Oral Therapies

PDE-5 Inhibitors (PDE-5i)

Endothelin Receptor Antagonists (ERA)

## PDE-5 Inhibitors

Medication	Indication	Dosing
Sildenafil	Improves exercise ability in early-stage PAH	20 mg PO TID
		10 mg IV TID (short-term use in patients unable to take PO)
Tadalafil	Improves exercise ability	40 mg PO daily
		– Initiate 20 mg if renal/hepatic impairment or concurrent ritonavir – Avoid if CrCL <30 mL/min

TID = three times daily; PO = by mouth; CrCL = creatinine clearance.  
US Food and Drug Administration [website]. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed February 28, 2018.

## Endothelin Receptor Antagonists

Medication	Indication	Dosing	Pharmacologic Properties and Other Special Considerations
Bosentan	Improves exercise ability and decreases rate of clinical worsening in WHO FC III-IV	62.5 mg PO BID, then 125 mg PO BID after 4 weeks	- Dual antagonist of ET-1 <sub>A</sub> and -1 <sub>B</sub> receptors - Tracleer® Access Program (REMS: LFTs, Hb, pregnancy at baseline; monthly LFTs and pregnancy tests; every 3 months Hb)
Bosentan (FDA Approval September 2017)	WHO group 1	32-mg tablet for oral suspension	Approved for pediatric patients aged 3 years and older with idiopathic or congenital PAH
Ambrisentan	WHO FC II-III	10 mg PO daily	- Selective ET-1 <sub>A</sub> antagonist - Letairis® Education and Access Program (REMS: LFTs, Hb, pregnancy at baseline; monthly pregnancy tests)
Macitentan	Delays progression of PAH	10 mg PO daily	- Tissue selective - Lipophilic - Dual antagonist of ET-1 <sub>A</sub> and -1 <sub>B</sub> receptors - Opsumit® (REMS: LFTs, Hb, pregnancy at baseline; monthly pregnancy tests)

BID = twice daily; REMS = risk evaluation and mitigation strategy; Hb = hemoglobin; LFTs = liver function tests; Hb = hemoglobin; FDA = US Food and Drug Administration.  
US Food and Drug Administration [website]. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed February 28, 2018.

## Macitentan

Primary and Secondary Endpoints for Events Related to PAH and Death

Endpoint	Placebo (N=250)	Macitentan 3 mg (N=250)	Macitentan 10 mg (N=242)	Macitentan 3 mg vs Placebo		Macitentan 10 mg vs Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
No. of Patients (%)							
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52-0.96)	.01	0.55 (0.32-0.76)	<.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46-0.97)	.01	0.50 (0.34-0.75)	<.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48-1.98)	.92	0.64 (0.29-1.42)	.20
Death due to PAH	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37-2.04)	.72	0.44 (0.16-1.25)	.07
Death from any cause by the end of the study	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65-1.67)	.83	0.77 (0.46-1.28)	.25

Pulido T, et al. *N Engl J Med*. 2013;369:809-818.

## Prostacyclins

Epoprostenol

Treprostinil

Iloprost



## Treprostinil

IV CADD-Legacy®  
Pump



SQ CADD-MS®3  
Pump



Tyvaso®  
Inhalation System



SQ MiniMed®  
Pump



Crono® Five pump



US Food and Drug Administration [website]. Medical Devices. <https://www.fda.gov/MedicalDevices/default.htm>. Accessed February 28, 2018.

## Iloprost

I-neb® AAD® System



AAD = adaptive aerosol delivery.  
US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&appno=021779>. Accessed February 28, 2018.

## Parenteral Prostacyclins

Medication	Indication	Dosing	Pharmacologic Properties and Other Special Considerations
<b>Epoprostenol IV</b>	WHO FC III-IV	2 ng/kg/min titrated to dose-limiting adverse effects (usual range, 20-40 ng/kg/min)	<ul style="list-style-type: none"> <li>- Half-life 4-6 minutes</li> <li>- Back-up cassette/pump</li> <li>- Protect from light</li> <li>- Ice pack (Flolan® only)</li> <li>- Requires reconstitution and further dilution (0.9% saline or sterile water; Veletr®; special diluent: Flolan®)</li> <li>- Every 24-hour cassette change</li> </ul>
<b>Treprostinil SC</b>	WHO FC III-IV	1.25 ng/kg/min titrated to dose-limiting adverse effects (usual range, 40-80 ng/kg/min)	<ul style="list-style-type: none"> <li>- Half-life 4 hours</li> <li>- Back-up pump</li> <li>- Stable at room temperature</li> <li>- SQ: Undiluted, every 72-hour syringe change</li> <li>- IV: Requires further dilution, every 48-hour cassette change</li> </ul>

US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Inhaled Prostacyclins

Medication	Indication	Dosing	Other Special Considerations
<b>Iloprost</b>	WHO FC III-IV	2.5-5 mcg given 6-9 times per day (maximum, 45 mcg/d)	<ul style="list-style-type: none"> <li>- Only administered via I-neb® AAD® System</li> <li>- Use higher concentration ampule (20 mcg/mL) for patients with extended treatment time or at 5-mcg dose</li> </ul>
<b>Treprostinil</b>	Increases walk distance in WHO FC III	<ul style="list-style-type: none"> <li>- 3 breaths QID</li> <li>- Titrate by 3 breaths every 1-2 weeks up to 9 breaths QID</li> </ul>	<ul style="list-style-type: none"> <li>- Only administered via Tyvaso® Inhalation System</li> </ul>

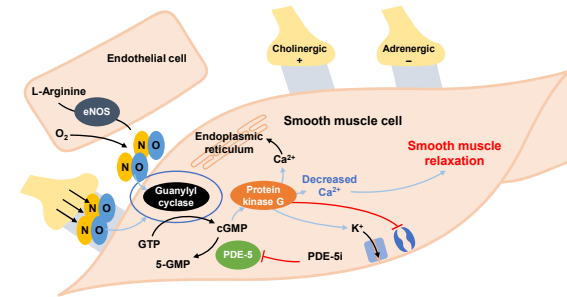
QID = four times daily.

US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Newer Oral Therapies

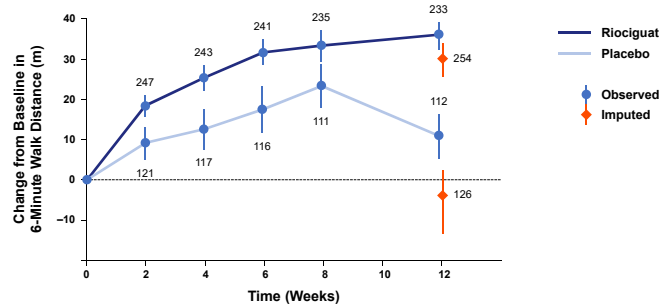
Riociguat  
Oral Treprostinil  
Selexipag

## Riociguat



eNOS = endothelial nitric oxide synthase; 5-GMP = guanosine 5'-monophosphate; PDE-5 = phosphodiesterase-5; PDE-5i = phosphodiesterase-5 inhibitor.  
US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Riociguat (cont)



Ghofrani H-A, et al. *N Engl J Med*. 2013;369:330-340.

## Riociguat (cont)

- Indicated to improve exercise capacity, WHO FC, and delay clinical worsening in patients with:
  - PAH
  - Persistent/recurrent chronic thromboembolic pulmonary hypertension (after surgery or for inoperable disease)
- Initiate 1 mg PO TID; titrate in 0.5-mg increments every 2 weeks up to 2.5 mg PO TID
  - Start 0.5 mg PO TID if risk for hypotension or with concomitant strong CYP and P-gp inhibitors
  - Avoid if CrCL <15 mL/min or if on hemodialysis
- Adempas® REMS program (teratogenicity)

CYP = cytochrome P450; P-gp = p-glycoprotein.  
US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Treprostinil Diolamine Extended Release

- Indicated to improve exercise capacity in patients with WHO FC II-III symptoms
- Initiate 0.25 mg PO BID or 0.125 mg PO TID
- Titrate by 0.125- to 0.5-mg PO increments BID to TID every 3 to 4 days or longer
- Maximum dosing per patient tolerability
- Administer with food to improve bioavailability
  - High calorie, high-fat meal

US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Selexipag

- Selective IP-receptor agonist
- Type of prostanoid receptor found in lungs (regulates vascular tone, platelet activity, immunologic responses)
- Similar mode of action to prostacyclin, but a non-prostanoid
- Approved to delay disease progression and reduce risk of hospitalization for patients with PAH
- Initiate 200 mcg PO BID and uptitrate weekly as tolerated to a maximum of 1600 mcg PO BID

US Food and Drug Administration [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.fda.gov/Drugs/default.htm>. Accessed February 28, 2018.

## Selexipag (cont)

Endpoints Related to PAH and Death

Endpoint	Placebo (N=562)	Selexipag (N=574)	Hazard Ratio (95% or 95% CI)	P Value
No. of Patients (%)				
<b>Primary endpoint: Composite of death or a complication related to PAH up to the end of the treatment period</b>				
All events	242 (41.6)	155 (27.0)	0.60 (0.46-0.78)	<.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH	2 (0.3)	1 (0.2)		
<b>Secondary endpoint: Death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period</b>				
All events	137 (23.5)	102 (17.8)	0.70 (0.54-0.91)	.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
<b>Secondary endpoint: Death up to the end of the study</b>				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63-1.18)	.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74-1.28)	.42

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

## Adverse Reactions

Medication/Class	Reaction
PDE-5i	Headache, dyspepsia, flushing, epistaxis, insomnia, hypotension, visual changes
Riociguat	Headache, dizziness, dyspepsia, gastroesophageal reflux, nausea, diarrhea, vomiting, hypotension, anemia, constipation, teratogenicity
ERAs	Headache, flushing, peripheral edema, nasal congestion, sinusitis, transaminitis, liver injury, anemia, teratogenicity
Prostacyclins	Nausea, vomiting, diarrhea, flushing, jaw pain, headache, rash, erythema, hypotension, leg pain – Inhaled: Cough, throat irritation
Selexipag	Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing

ERA = endothelin receptor antagonist.  
Gallè N, et al. *Eur Heart J*. 2016;37:67-119.

## Parenteral Prostacyclins: Line-Related Complications

- **SQ:** Injection-site pain, swelling
  - Preemptive site management (eg, topical analgesics)
- **IV:** Catheter-related infection, bacteremia, thrombosis
  - ↑ risk of Gram-negative infection (treprostinil > epoprostenol)
- Need for extensive education/training, support

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

## Drug Interactions

Medication/Class	Interaction
<b>PDE-5i</b>	Strong CYP3A4 inhibitors/inducers, nitrates, alpha-blockers, alcohol
<b>Riociguat</b>	Strong CYP and P-gp inhibitors/inducers, PDE-5is, non-specific PDE inhibitors (eg, theophylline, dipyridamole), nitrates, antacids, smoking
<b>ERAs</b>	Strong CYP3A4 and CYP2C19 inhibitors/inducers, warfarin, oral contraceptives – <i>Bosentan</i> : Cyclosporine, glyburide
<b>Prostacyclins</b>	Vasodilators, antiplatelets, anticoagulants – <i>Treprostinil</i> : Gemfibrozil, rifampin
<b>Selexipag</b>	Strong CYP2C8 inhibitors

CYP = cytochrome P450; P-gp = p-glycoprotein.  
Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

## Adjunctive Treatments

- Diuretics
- Digoxin
- Oxygen
- Warfarin

## Patient Case

- HL is a 43-year-old mother of three who presented with a 2-month history of dyspnea on exertion and fatigue consistent with class II to class III symptoms
- She reports a 1-year use of phentermine for weight loss prior to symptom onset
- She also reports that her mother had PAH and died at the age of 47 years
- She was diagnosed with PAH (heritable vs drug-induced) based on RHC

PAH = pulmonary arterial hypertension; RHC = right heart catheterization.

## Patient Case (cont)

Which medication would you recommend for HL?

1. PDE-5i
2. Epoprostenol
3. ERA
4. PDE-5i + ERA
5. Inhaled prostacyclin

## Treatment Guidelines

Initial Therapy with PAH-Approved Drugs

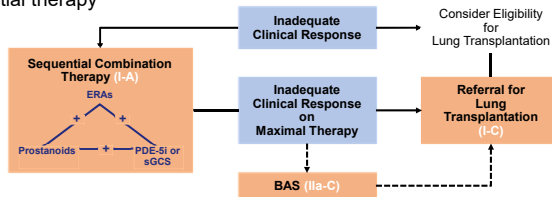
Recommendation	Evidence <sup>a</sup>	WHO FC II	WHO FC III	WHO FC IV
I	A or B	Ambrisentan Bosentan Macitentan <sup>b,c</sup> Riociguat <sup>b</sup> Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV Iloprost inhaled Macitentan <sup>b,c</sup> Riociguat <sup>b</sup> Sildenafil Tadalafil Treprostinil SC inhaled <sup>d</sup>	Epoprostenol IV
IIa	C		Iloprost IV <sup>b</sup> Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled and IV <sup>b</sup> Macitentan <sup>b,c</sup> Riociguat <sup>b</sup> Sildenafil Tadalafil Treprostinil SC, IV, inhaled <sup>d</sup>
IIb	B		Beraprost <sup>b</sup>	
	C		Initial Combination Therapy	Initial Combination Therapy

Orange: Morbidity and mortality as primary endpoint in randomized controlled study or reduction in all-cause mortality (prospectively defined).

<sup>a</sup>Level of evidence is based on the WHO-FC of the majority of the patients of the studies. <sup>b</sup>Approved only: By the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost IV); in Japan and S. Korea (beraprost). <sup>c</sup>Positive opinion for approval of the CHMP of EMA. Gallé N, et al. *J Am Coll Cardiol*. 2013;62:D60-D72.

## Approaches to the Treatment of PAH

### Sequential therapy



### Up-front combination therapy

- AMBITION trial (tadalafil + ambrisentan vs monotherapy with either)
- Hazard ratio, 0.50 (95% CI, 0.35-0.72;  $P < .001$ ) for composite of clinical failure events in favor of combination group vs pooled monotherapy

sGCS = soluble guanylate cyclase stimulator; BAS = balloon atrial septostomy.  
Gallé N, et al. *J Am Coll Cardiol*. 2013;62(25 suppl): D60-D72.

## Specialty Pharmacy

- Complex and costly medications/delivery systems
- Types of services
  - Clinical counseling and support
  - Local nursing support and training
  - Prior authorization
  - Medication delivery

Kaas S, et al. *Res Soc Admin Pharm*. 2012;8(3):253-257. ReCept pharmacy [website]. <http://receptrx.com/prescriber/>. Accessed April 18, 2018.

## Medication Safety

- Ensure communication across transitions of care
- Policy/protocol/guideline development and oversight
- Prostacyclin vigilance
  - Determine essential order details for prostacyclins: type of agent, route, pump, timing of next dose, dosing weight, current dose, titration schedule, vial concentration (treprostinil) or vial size (epoprostenol), amount of medication and diluent for mixing, type of diluent, infusion rate, back-up cassette availability (epoprostenol)

Coons JC, et al. *Am J Health-Syst Pharm*. 2013;70:1716-1723.

## Patient Counseling

- Expectations from treatment/goals of care
- Dosing/administration/product preparation
- Catheter and line care
- Adherence
- Specialty pharmacy and nursing contact
- Maintaining accurate medication list
- Updated dosing sheet from specialty pharmacy
- Monitoring and follow-up
- Symptom recognition
- Emotional support
- Adverse events
- Health maintenance
  - Diet/exercise
  - Immunizations
  - Pregnancy/contraception

Poms A, et al. Support care for the pulmonary hypertension patient. In: Maron B, et al (eds). *Pulmonary Hypertension*. Cham, Switzerland: Springer; 2016.

## PAH “Clinical Pearls”

- Improved clinical outcomes have been realized in PAH through advancements in pharmacotherapy
- There are now 14 FDA-approved medication formulations with more in the pipeline
- Pharmacists are well-positioned, and essential, to safe and effective PAH care in a team-based setting

## Questions?

Thank you for your attention!

# Overcoming Challenges in the Management of Invasive Fungal Infections



This session is supported by an educational grant from Astellas.

CELEBRATING  
10  
YEARS

## Faculty

**James S. Lewis II, PharmD, FIDSA**

ID Clinical Pharmacy Coordinator  
Oregon Health and Science University  
Departments of Pharmacy and Infectious Diseases  
Portland, Oregon

## Faculty Disclosure

**Dr. Lewis:** Consultant—Accelerate Diagnostics, Allergan, Astellas, The Medicines Company, Merck & Co., Inc.

## Learning Objectives

- Describe the current challenges associated with the management of IFI
- Compare clinical data of available antifungal therapies, including differences in the spectrum of activity, mechanisms-of-action, PK and PD, tissue penetration, and adverse effects
- Implement timely and informed clinical decisions that incorporate the latest evidence with respect to prophylactic, empiric, preemptive, and targeted antifungal treatment
- Lead the healthcare team in ensuring appropriate IFI treatment monitoring and modification, medication reconciliation, and prevention of drug toxicities and interactions

IFI = invasive fungal infection; PK = pharmacokinetics; PD = pharmacodynamics.

## Patient Case

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Receiving piperacillin-tazobactam and vancomycin
- Doing well in the surgical intensive care unit until hospital day 5
- Increasing fevers, increasing white blood cell counts
- Abdominal imaging suggests a new fluid collection
- What organisms are you concerned about?

## Pathogens Associated with Healthcare-Associated Infections

Pathogen	All Healthcare-Associated Infections (N=504) No. (%)	Pneumonia (N=110)	Surgical Site Infections (N=110)	Gastrointestinal Infections (N=86)	Urinary Tract Infections (N=65)	Bloodstream Infections (N=50)
<i>Clostridium difficile</i>	61 (12.1)	0	0	61 (70.9)	0	0
<i>Staphylococcus aureus</i>	54 (10.7)	18 (16)	17 (16)	1 (1)	2 (3)	7 (14)
<i>Klebsiella pneumoniae</i> or <i>Klebsiella oxytoca</i>	50 (9.9)	13 (12)	15 (14)	1 (1)	15 (23)	4 (8)
<i>Escherichia coli</i>	47 (9.3)	3 (3)	14 (13)	1 (1)	18 (28)	5 (10)
<i>Enterococcus</i> species	44 (8.7)	2 (2)	16 (15)	5 (6)	11 (17)	6 (12)
<i>Pseudomonas aeruginosa</i>	36 (7.1)	14 (13)	7 (6)	1 (1)	7 (11)	2 (4)
<i>Candida</i> species	32 (6.3)	4 (4)	3 (3)	3 (4)	3 (5)	11 (22)

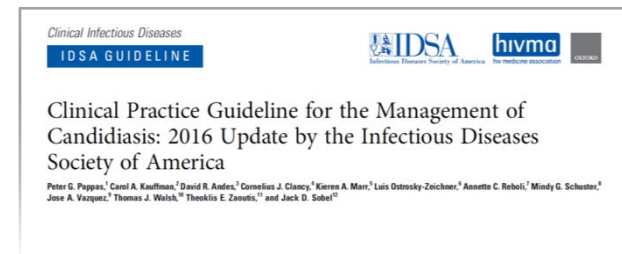
Magill SS, et al. *N Engl J Med*. 2014;370:1198.

## The Impact of Candidemia

- Fourth most common bloodstream isolate
- Leading fungal pathogen in US hospitals
- 14.5% attributable increase in mortality in adults
- 10.1-day increased length of stay
- Approximately \$60,000 increase in hospital charges

Zaoutis TE, et al. *Clin Infect Dis*. 2005;41(9):1232-1239. Weinberger M, et al. *J Hosp Infection*. 2005;61(2):146-154. Billir SP, et al. *Future Microbiol*. 2015;10:1133-1144. Moran C, et al. *Am J Infect Control*. 2010;38:78-80.

## New Guidelines



Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-e50.



## Invasive Candidiasis: Who Is at Risk?

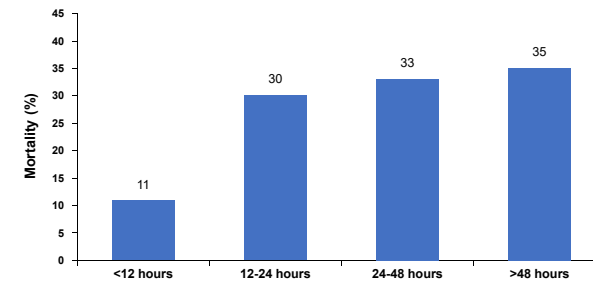
### Risk Factors

- Central venous catheters
- Candida* species colonization
- Increasing severity of illness
- Exposure to broad-spectrum antibiotics
- Recent major surgery, especially abdominal
- Necrotizing pancreatitis
- Hemodialysis
- Parenteral nutrition
- Corticosteroids

- A subset of postsurgical patients may be at uniquely high risk of candidiasis
  - Recurrent gastrointestinal perforation
  - Anastomotic leaks
  - Acute necrotizing pancreatitis

Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-e50.

## Candidemia: Time to Initiation of Therapy and Mortality



Is your team thinking about *Candida* species in high-risk patients?

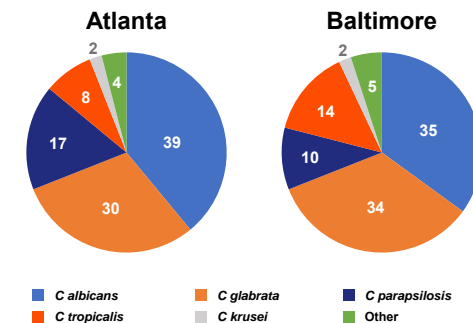
Morrell M, et al. *Antimicrob Agents Chemother*. 2005;49:3640-3645.

## General Susceptibility Patterns of *Candida* Species

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Candins	AmB
<i>Candida albicans</i>	S	S	S	S	S	S
<i>Candida glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I
<i>Candida tropicalis</i>	S	S	S	S	S	S
<i>Candida parapsilosis</i>	S	S	S	S	S to R	S
<i>Candida krusei</i>	R	S-DD to R	S	S	S	S to I

AmB = amphotericin B; S = susceptible; S-DD = susceptibility-dose dependent; R = resistant; I = intermediate.  
Pappas PG, et al. *Clin Infect Dis*. 2009;48(5):503-535.

## Current *Candida* Species Epidemiology



Cleveland AA, et al. *PLoS One*. 2015;10(3):e0120452.

## Patient Case (cont)

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Receiving piperacillin-tazobactam and vancomycin
- Results from blood cultures drawn on hospital day 5 now positive for yeast
- What therapy should this patient receive?

## Candidemia in Non-Neutropenic Patients

- Echinocandin is recommended as initial therapy
  - Strong recommendation; high-quality evidence
- Fluconazole, IV or PO, 800-mg (12 mg/kg) load, then 400 mg (6 mg/kg) daily is an acceptable alternative in select patients
  - Not critically ill
  - Not likely to have a fluconazole-resistant *Candida* species
    - Strong recommendation; high-quality evidence

IV = intravenous; PO = oral.  
Pappas PG, et al. *Clin Infect Dis*. 2016;62:e1-e50.

## Amphotericin B vs Fluconazole vs Echinocandin: Which One Is Best for Candidemia?

- Patient-level review of recent randomized trials for candidemia
- Data for all 3 classes of drugs used
- Data from 1915 patients, 7 trials
- Overall mortality rate was 31.4%
- Treatment success rate was 67.4%

Andes DR, et al. *Clin Infect Dis*. 2012;54(8):1110-1122.

## Bad Prognostic Signs

Predictors of Mortality using Logistic Regression

Predictor	OR	95% CI
Increasing age	1.01	1.00-1.02
Higher APACHE II score	1.11	1.08-1.14
Immunosuppressive therapy	1.69	1.18-2.44
Infection with <i>C tropicalis</i>	1.64	1.11-2.39

OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation.  
Andes DR, et al. *Clin Infect Dis*. 2012;54(8):1110-1122.

## Predictors of a Good Outcome

- Removal of central venous catheter
  - OR=0.50, 95% CI=.35-.72,  $P=.0001$
- Treatment with an echinocandin
  - OR=0.65, 95% CI=.45-.94,  $P=.02$
- Similar findings using the clinical success endpoint

Assessment of lines should be a consideration for the entire team!

Andes DR, et al. *Clin Infect Dis*. 2012;54(8):1110-1122. Clancy CJ, et al. *Clin Infect Dis*. 2012;54(8):1123-1125.

## Prophylaxis/Early Empiric Therapy

JAMA Clinical Evidence Synopsis

### Associations of Antifungal Treatments With Prevention of Fungal Infection in Critically Ill Patients Without Neutropenia

Andrea Cortegiani, MD, Vincenzo Russo, MD, Antonino Giarratano, MD

**CLINICAL QUESTION** Are antifungal agents associated with lower rates of mortality and invasive fungal infections when administered before definitive diagnosis of an invasive fungal infection in critically ill patients without neutropenia?

**BOTTOM LINE** Antifungal treatment administered prior to diagnosis of an invasive fungal infection is not associated with either higher or lower rates of all-cause mortality. Antifungal treatment in this setting is associated with lower rates of invasive fungal infections compared with placebo or no intervention in critically ill patients without neutropenia, but the quality of the evidence is low.

No decrease in mortality, fewer invasive fungal infections...  
very unrewarding!

Cortegiani A, et al. *JAMA*. 2017;317:311-312.

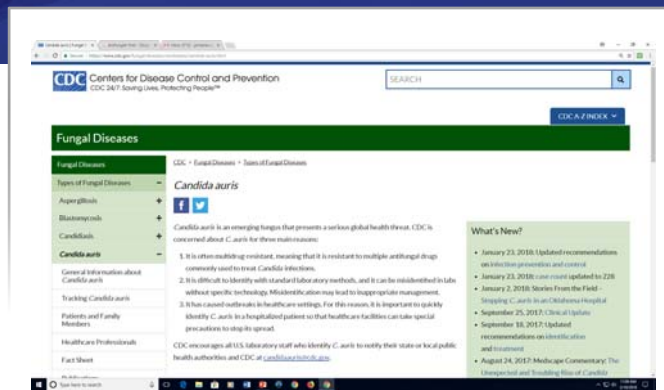
## Susceptibility Testing

- Testing for azole susceptibility is recommended for:
  - All bloodstream isolates
  - Other clinically relevant *Candida* species isolates
- Testing for echinocandin susceptibility should be considered:
  - In patients who have had prior treatment with an echinocandin
  - Among those who have had infection with *C glabrata* or *C parapsilosis* (strong recommendation; low-quality evidence)

Pappas PG, et al. *Clin Infect Dis*. 2016;62:e1-e50.

## Patient Case (cont)

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Patient returns to the operating room for repair of the leak and drainage of the abscess
- She has been receiving micafungin for 6 days
- She has improved clinically
- Her blood cultures grew *C albicans*
- Should she have received empiric therapy?



CDC [website]. Fungal Diseases. <https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris.html>. Accessed February 8, 2018.

## Candida Species: Conclusions

- Echinocandins are first-line choice in 2018
- Pull the lines when possible
- Epidemiology appears stable
- Know your institutional epidemiology
- Emergence of multidrug-resistant *C glabrata*?

## Aspergillus Species and the Azoles

Clinical Infectious Diseases  
IDSA GUIDELINE

IDSA  
Infectious Diseases Society of America

hivma  
the medicine association

### Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,<sup>1,2</sup> George R. Thompson III,<sup>2</sup> David W. Denning,<sup>3</sup> Jay A. Fishman,<sup>4</sup> Susan Hadley,<sup>5</sup> Raulo Herberich,<sup>6</sup> Dimitrios P. Kontogiannis,<sup>7</sup> Kieren A. Marr,<sup>8</sup> Vicki A. Morrison,<sup>9</sup> M. Hong Nguyen,<sup>10</sup> Brian H. Segal,<sup>11</sup> William J. Steinbach,<sup>12</sup> David A. Stevens,<sup>13</sup> Thomas J. Walsh,<sup>14</sup> John R. Wingard,<sup>15</sup> Jo-Anne H. Young,<sup>16</sup> and John E. Bennett<sup>17,18</sup>

- Primary treatment with voriconazole still recommended
- Initiate therapy early
- Alternatives to voriconazole for primary therapy
  - Isavuconazole
  - Lipid formulations of AmB
- Echinocandins are NOT recommended for primary therapy

Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-e60.

## Patient Case

- A 53-year-old man with acute myeloid leukemia
- Normal cytogenetics
- Admitted for induction therapy
- Planning to be followed up to undergo a stem-cell transplantation
- What fungal infections do you need to consider?
- what drug classes are options?

## Voriconazole: Strengths

- The current gold standard for IA?
- Broad spectrum – but NO mucormycosis
- IV and PO formulations
- Oral formulation now generic
- High oral bioavailability
- Penetrates human brain tissue and abscess material, achieving peak concentrations similar to or even exceeding those seen in plasma
- Agent of choice for central nervous system aspergillosis

IA = invasive aspergillosis.  
Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-60. Dodds-Ashley ES, et al. *Clin Infect Dis*. 2006;43:S28-S39. Felton T, et al. *Clin Microbiol Rev*. 2014;27(1):68-88.

## Voriconazole: Weaknesses

- Increasing concern over the risk of skin cancer
- Is the bioavailability as good as we thought?
- Cytochrome P450 nightmares continue
- When and when not to weight-based dose
- Toxic at high levels?
  - Liver function tests
  - Hallucinations

Kuklinski LF, et al. *J Am Acad Dermatol*. 2017;77(4):706-712. Pascual A, et al. *Clin Infect Dis*. 2012;55(3):381-390.

## Posaconazole: Strengths

- Broad-spectrum azoles (>vori – zygomycetes)
- Mortality benefit in select populations
- Well-tolerated
- Solid tablet formulations and IV formulations
  - No treatment indications
  - Enhanced bioavailability solid oral dosage form – daily dosing!
  - IV (highly wallet toxic!)
- Penetrates into the inflamed eye
- Concentration within the human dermis comparable to that in plasma

Krishna G, et al. *J Antimicrob Chemother*. 2012;67(11):2725-2730. Felton T, et al. *Clin Microbiol Rev*. 2014;27(1):68-88.

## Posaconazole: Weaknesses

- Kill the oral suspension! – Dosing differences
- Tablets are a marked improvement
- Once daily! Tablets and IV only!
- Saturable absorption – Not an issue with tablets?
- Erratic absorption – Only with the liquid
- Drug interactions – CYP3A4
- pH issues – Fewer with tablets

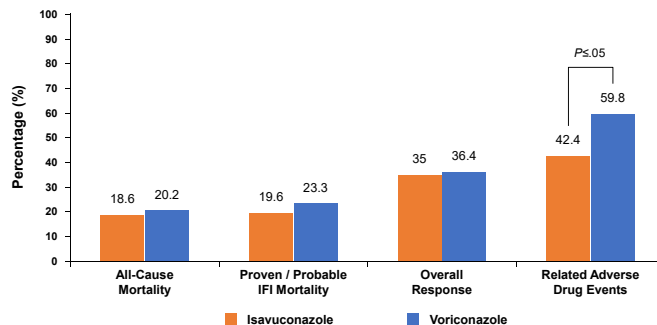
Pham A, et al. *Mycoses*. 2016;59:226-233.

## Isavuconazole

- Spectrum very similar to posaconazole
- Broad in vitro activity against a range of medically important fungi (eg, *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*)
- Once daily and a prodrug – Loading doses required
- IV and PO
- No cyclodextrin in the IV
- Treatment indications – Very little prophylaxis data
- Indicated for the treatment of mucormycosis
- Issues with *Candida* species data

US Food and Drug Administration [website]. Drugs. [https://google2.fda.gov/search?q=isavuconazole&client=FDAGov&site=FDAGov&lr=&proxystylesheet=FDAGov&requiredfields=-archive%3AYes&output=xml\\_no\\_dtd&getfields=](https://google2.fda.gov/search?q=isavuconazole&client=FDAGov&site=FDAGov&lr=&proxystylesheet=FDAGov&requiredfields=-archive%3AYes&output=xml_no_dtd&getfields=). Accessed February 13, 2018. Warn PA, et al. *Antimicrob Agents Chemother*. 2009;53(8):3453-3461.

## Voriconazole vs Isavuconazole: IA and Other Mold

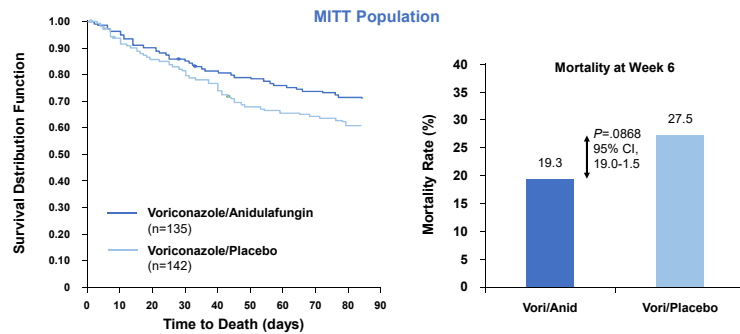


Maertens JA, et al. *Lancet*. 2016;387:760-769.

## Patient Case (cont)

- A 53-year-old man with acute myeloid leukemia
- Normal cytogenetics
- Admitted for induction therapy
- Patient underwent induction therapy, neutrophils recovered on day 26, and patient was discharged on day 29
- Readmitted to undergo allogeneic (brother) hematopoietic stem-cell transplantation, which was successful, and then discharged home
- Readmitted with pleuritic chest pain, dry cough, and new 1-cm nodule noted on chest computed tomographic scan

## Voriconazole + Anidulafungin vs Voriconazole Monotherapy for IA: MITT Population Crashing



MITT = modified intent-to-treat.  
Marr KA, et al. Presented at 22nd European Congress of Clinical Microbiology and Infectious Disease, April 2, 2012, London, United Kingdom. Abstract LB 8212. Marr KA, et al. *Ann Intern Med*. 2015;162(2):81-89. Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-e60.

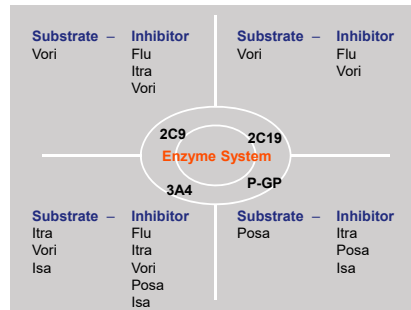
## The Anti-*Aspergillus* Azoles: Toxicity and Monitoring

- Voriconazole is not benign
  - Unpredictable pharmacokinetics
  - Skin cancer
  - Hallucinations
  - Monitoring required: Trough >1-6
  - Do all practitioners seeing the patient know what to look for?
- Posaconazole tablets: Do they even need monitoring?
- Isavuconazole: Role should be clarified by further studies

Williams K, et al. *Clin Infect Dis*. 2014;58:997-1002. Moon WJ, et al. *Clin Infect Dis*. 2014;59:1237-1245. Pascual A, et al. *Clin Infect Dis*. 2012;55:381-390. Andes D, et al. *Antimicrob Agent Chemother*. 2009;53:24-34. Pham A, et al. *Mycoses*. 2016;59:226-233. Miceli MH, et al. *Clin Infect Dis*. 2015;61(10):1558-1565.

## Drug Interaction Challenges: An Issue for the Healthcare Team

- "New information is emerging rapidly, and thus, this review is by its very nature incomplete"
- Medication reconciliation has increased in importance since the passage of the Patient Protection and Affordable Care Act in 2010
- The role of each healthcare provider, including the pharmacist, in the medication reconciliation continuum should be clearly defined
- Medication assessment and reconciliation by pharmacists 3-7 days post-discharge can decrease readmissions and provide cost savings



P-GP = P-glycoprotein.  
Bruggemann RJM, et al. *Clin Infect Dis*. 2009;48:1441. US Food and Drug Administration. Advisory Committee Briefing Document. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/UCM430748.pdf>. Accessed February 29, 2016. Splawski J, et al. *P T*. 2016;41(3):176-178. Kilcup M, et al. *J Am Pharm Assoc*. 2013;53:78-84.

## So...Advanced Azoles 2018

- And then there were 3:
  1. Voriconazole
  2. Posaconazole
  3. Isavuconazole
- How different are they?
  - Excellent tissue penetration
- Do the indications matter?
- How different are the spectrums and pharmacokinetics/pharmacodynamics?
- Are they interchangeable?

Questions?



## Tackling the Complexities of Biosimilars Across Pharmacy Settings



This session is supported by an educational grant from Sandoz.

CELEBRATING  
10  
YEARS

## Faculty

**Steven Lucio, PharmD, BCPS**

Associate Vice President  
Center for Pharmacy Practice Excellence  
Vizient  
Irving, Texas

## Disclosures

**Dr. Lucio:** Employee - Vizient

## Learning Objectives

- Outline the requirements for biosimilars approval such as the clinical data package, totality of evidence, extrapolation of data, interchangeability, and substitution
- Evaluate the clinical data supporting the safety, efficacy, biosimilarity, and interchangeability of approved and late-stage biosimilars
- Describe the impact of current and emerging regulatory and legal requirements on biosimilar interchangeability designation, switching/comparability studies, pharmacovigilance, product tracking, and accessibility
- Integrate new and emerging biosimilars into clinical care plans, systems-based processes, formulary discussions, and provider/patient communication strategies

## Phases of Biosimilar Market Development



G-CSF = granulocyte-colony stimulating factor.

## Biosimilar Approvals to Date

	Product	Manufacturer	Date Approved	Date Marketed
1	Zarxio® (filgrastim-sndz)	Sandoz	3/6/2015	9/3/2015
2	Inflectra® (infliximab-dyyb)	Celltrion/Pfizer	4/5/2016	11/2016
3	Erelzi™ (etanercept-szsz)	Sandoz	8/30/2016	?
4	Amjevita® (adalimumab-atto)	Amgen	9/23/2016	1/31/2023 (proposed)
5	Renflexis™ (infliximab-abda)	Samsung/Merck	4/21/2017	7/24/2017
6	Cyltezo® (adalimumab-adbm)	Boehringer Ingelheim	8/29/2017	?
7	Mvasi™ (bevacizumab-awwb)	Amgen/Allergan	9/14/2017	?
8	Ogivri™ (trastuzumab-dkst)	Mylan	12/1/2017	?
9	Ixifi® (infliximab-qbtx)	Pfizer	12/13/2017	?
10	Retacrit™ (epoetin alfa-epbx)	Pfizer	5/15/2018	Pending
11	Fulphila™ (pegfilgrastim-jmdb)	Mylan	6/4/2018	Pending
12	Nivestym™ (filgrastim-aafi)	Pfizer	7/20/2018	Pending

FiercePharma [website]. <https://www.fiercepharma.com/pharma/abbvie-s-humira-patents-hold-up-as-amgen-settles-2023-biosim-launch>. Accessed January 17, 2018. Drugs@FDA Approved Products [website]. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed August 27, 2018.

## Known Biosimilar Pipeline for Remainder of 2018

International Nonproprietary Name	Manufacturer	Application Submitted	Estimated FDA Approval Date
Trastuzumab (CT-P6)	Teva and Celltrion	5/2017	3/2018 <sup>a</sup>
Trastuzumab (ABP 980)	Amgen and Allergan	7/2017	5/2018 <sup>a</sup>
Rituximab (GP2013)	Sandoz	7/2017	5/2018 <sup>a</sup>
Trastuzumab (PF-05280014)	Pfizer	7/2017	5/2018 <sup>a</sup>
Filgrastim	Adello Biologics	7/2017	5/2018?
Trastuzumab (SB3)	Samsung Bioepis and Merck	10/2017	10/2018
Rituximab (CT-P10)	Teva and Celltrion	5/2018	11/2018
Adalimumab (GP2017)	Sandoz	11/2017	11/2018
Pegfilgrastim (CHS-1701)	Coherus	5/2018	11/3/2018

<sup>a</sup>Delayed due to receipt of complete response letter.

FDA = US Food and Drug Administration.

Pink Sheet [website]. <https://pink.pharmaintelligence.informa.com/product-reviews-and-approvals/fda-performance-tracker>. Accessed August 31, 2018.

## Biosimilars: Legal and Regulatory Updates

## FDA Biosimilar Action Plan



- 11 actions identified by the US Food and Drug Administration to:
  - Improve the efficiency of biosimilar and interchangeable biologic development and approval
  - Maximize scientific and regulatory clarity for the biosimilar development community
  - Increase understanding of biosimilars among patients, clinicians, and payors
  - Reduce gaming of FDA requirements or other attempts to unfairly delay competition
- Open public hearing: September 4, 2018

US Food and Drug Administration. Biosimilars action plan: balancing innovation and competition. July 2018:1-9. <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf>.

## Legal Updates

- AbbVie and Amgen settlement
  - AbbVie to grant nonexclusive patent licenses to Amgen
  - Amgen can launch biosimilar adalimumab in Europe on October 16, 2018, and in the United States on January 31, 2023
- AbbVie and Samsung Bioepis agreement
  - If approved, biosimilar can launch June 30, 2023
- Pfizer lawsuit against Johnson & Johnson due to anticompetitive practices related to Remicade®
- Amgen awarded \$70 million for Pfizer/Hospira biosimilar infringing Epogen® patents
- Many other legal issues remain throughout the court system

Pink Sheet [website]. <https://pink.pharmintelligence.informa.com>. Accessed February 5, 2018. Reuters [website]. Health News. Mathias T. April 5, 2018. <https://www.reuters.com/article/us-abbvie-biogen/abbvie-samsung-bioepis-in-deal-humira-biosimilar-u-s-release-in-2023-idUSKCN1HC1SP>. Accessed April 6, 2018.

## What Have We Learned from Biosimilars Approved to Date?

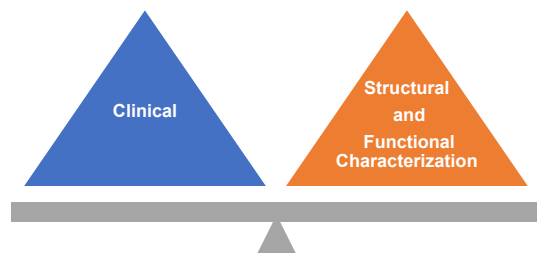
## Progression of Biosimilar Approvals

	Zarxio	Inflectra	Erelzi	Amjevita
<b>Name</b>	<ul style="list-style-type: none"> <li>• Filgrastim-sndz (place holder)</li> <li>• Proposed name: filgrastim-bfim</li> </ul>	<ul style="list-style-type: none"> <li>• Infliximab-dyyb</li> </ul>	<ul style="list-style-type: none"> <li>• Etanercept-szzs</li> </ul>	<ul style="list-style-type: none"> <li>• Adalimumab-atto</li> </ul>
<b>Indications studied</b>	<ul style="list-style-type: none"> <li>• Myelosuppressive chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• Ankylosing spondylitis</li> </ul>	<ul style="list-style-type: none"> <li>• Plaque psoriasis</li> </ul>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• Plaque psoriasis</li> </ul>
<b>Indication coverage</b>	<ul style="list-style-type: none"> <li>• All non-orphan indications</li> </ul>	<ul style="list-style-type: none"> <li>• All non-orphan indications</li> </ul>	<ul style="list-style-type: none"> <li>• All indications*</li> <li>• No weight-based dosing for children &lt;63 kg (product only available in prefilled syringe)</li> </ul>	<ul style="list-style-type: none"> <li>• All non-orphan indications</li> </ul>

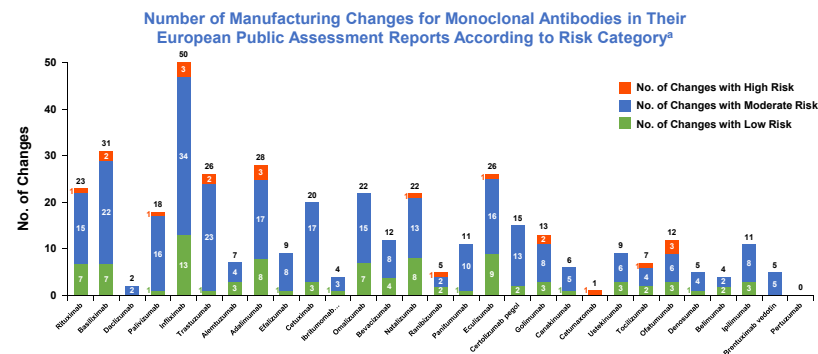
\*Since approval, Sandoz has requested removal of psoriatic arthritis and plaque psoriasis indication from label to avoid patent infringement.

US FDA [website]. <https://wayback.archiveit.org/7993/20170404153112/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM436387.pdf>. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf>. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510493.pdf>. Accessed February 5, 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2018/761042Orig1s001ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/761042Orig1s001ltr.pdf). Accessed April 6, 2018.

## Biosimilar Balancing Act



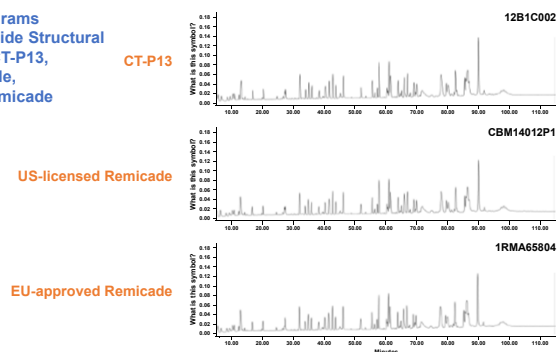
## Originator Biologic Manufacturing Changes



\*During the search period, all non-proprietary names relate only to the trade named medicines listed in Table 1.  
Vezér B, et al. *Curr Med Res Opin.* 2016;32(5):829-834. Vizient Presentation. August 2017. Confidential Information.

## Infliximab-dyyb Analytic Characterization

RP-HPLC Chromatograms from the Tryptic Peptide Structural Characterization of CT-P13, US-licensed Remicade, and EU-approved Remicade



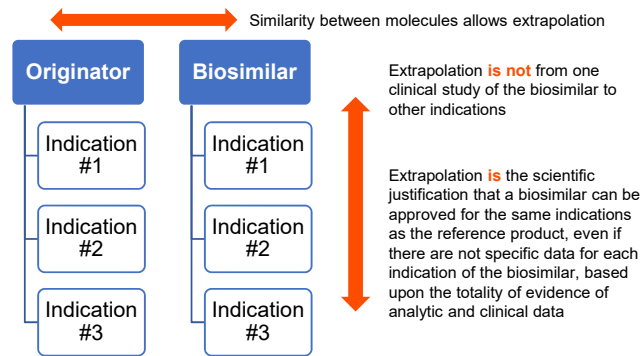
RP-HPLC = reverse phase-high-performance liquid chromatography.  
US FDA. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf>. Accessed February 5, 2018.

## The Efficiency of Bridging

Study (Dates)	Design (Objectives)	Patient Population (Total Number)	Treatment Arms	No. per Arm
CT-P13 3.1 (Global, ex-US) 54 weeks (12/10 to 07/12)	R, DB, PG comparative clinical study: Efficacy, safety, PK, immunogenicity	Moderate to severe RA, MTX-IR N=606	CT-P13 3 mg/kg + MTX EU-approved infliximab	n=302 n=300
CT-P13 1.1 (Global, ex-US) 54 weeks (12/10 to 07/12)	R, DB, PG PK, efficacy, safety, immunogenicity	Moderate to severe AS N=250	CT-P13 5 mg/kg EU-approved infliximab	n=128 n=122
CT-P13 1.4 Single Dose (10/13 to 02/14)	R, DB, PG, SD 3-way PK bridging: PK, safety, immunogenicity	Healthy volunteers N=213	CT-P13 5 mg/kg EU-approved Remicade 5 mg/kg US-licensed Remicade 5 mg/kg	n=71 n=71 n=71

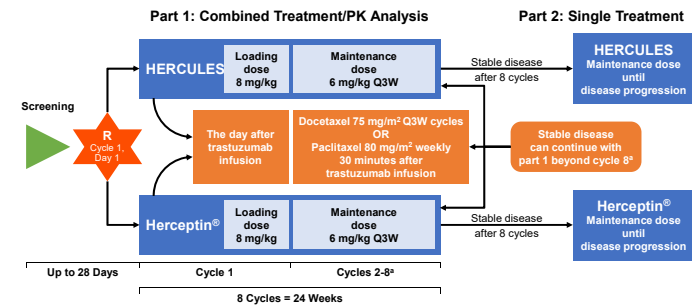
R = randomized; DB = double blind; PG = parallel-group; PK = pharmacokinetics; RA = rheumatoid arthritis; MTX = methotrexate; AS = ankylosing spondylitis; SD = single dose.  
[www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf). Accessed January 20, 2017.

## Understanding Extrapolation



McCamish M, et al. *Clin Pharmacol Ther.* 2015;97(3):215-217.

## Clinical Trial Design: Biosimilar Trastuzumab (HER2-positive, Metastatic Breast Cancer)



\*Continue 3-week cycles; if stable disease after 8 cycles, can continue combination treatment on part 1 at investigator's discretion. HERCULES = Herceptin, Cyclophosphamide, and Epirubicin trial; R = Randomization (within 3 days prior to cycle 1, day 1). US FDA [website]. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566369.pdf>. Accessed February 5, 2018.

## ORR (Biosimilar vs Originator)

ORR per Central Review at Week 24, ITT1 Population

	MYL-14010 + Taxane (N=230)	EU-Herceptin + Taxane (N=228)
Complete response (CR), n (%)	4 (2)	0
Partial response (PR), n (%)	157 (68)	146 (64)
Stable disease (SD), n (%)	48 (21)	49 (21)
Progressive disease (PD), n (%)	9 (4)	20 (9)
N/A, n (%)	12 (5)	13 (6)
ORR, n (%)	161 (70)	146 (64)
Ratio of ORR (MYL-14010 vs EU-Herceptin)	1.09	
90% CI	(0.98, 1.22)	

ORR ratio = 1.09, well within predefined range of 0.81 to 1.24

ORR = overall response rate; CI = confidence interval.  
FDA analysis of data from the Applicant 351(k) BLA submission. US FDA [website]. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566369.pdf>. Accessed February 5, 2018.

## Progression of Biosimilar Approvals

	Mvasi	Ogivri
Name	• bevacizumab-awwb	• trastuzumab-dkst
Indications studied	• Advanced/metastatic non-small cell lung cancer	• Patients with HER-2 positive metastatic breast cancer
Indication coverage	• Metastatic colorectal cancer • Non-squamous non-small cell lung cancer • Glioblastoma • Metastatic renal cell carcinoma • Cervical cancer	• Treatment of HER-2 overexpressing breast cancer • Treatment of HER-2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Indications not covered	• Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is platinum-resistant or platinum-sensitive (orphan exclusivity)	• None; all orphan exclusivity has expired

Bevacizumab-awwb prescribing information [website]. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/761028s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761028s000lbl.pdf). US FDA [website]. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566365.pdf>. Bevacizumab prescribing information [website]. [https://www.gene.com/download/pdf/avastin\\_prescribing.pdf](https://www.gene.com/download/pdf/avastin_prescribing.pdf). Trastuzumab prescribing information [website]. [https://www.gene.com/download/pdf/herceptin\\_prescribing.pdf](https://www.gene.com/download/pdf/herceptin_prescribing.pdf). Accessed February 5, 2018.

## Biologic Naming, Biosimilar Switching, Substitution, and Interchangeability

### What's in a Name?

- **Two names for biologics**

- Core name (eg, infliximab)
- Proper name = core name plus 4-letter suffix (eg, infliximab-dyyb)
  - Suffix must be unique and devoid of meaning
- Will ultimately apply to all biologics

- **Why?**

- Prevent inadvertent substitution
- Improve pharmacovigilance
- Encourage use of FDA-designated suffixes
- Advance accurate perceptions about biologics

US FDA [website]. [www.fda.gov/downloads/drugs/guidances/ucm459987.pdf](http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf). Accessed February 5, 2018.

### Naming in Practice

Current	Proposed
Filgrastim	Filgrastim-jcwp
Filgrastim-sndz	Filgrastim-bflm
Tbo-filgrastim	Filgrastim-vkzt
Epoetin alfa	Epoetin alfa-cgkn
Infliximab	Infliximab-hjmt
Pegfilgrastim	Pegfilgrastim-ljfd

- No timeline for implementation of proposed proper names for existing products
- However, have seen application to novel biologics (eg, Helimbra® – emicizumab-kxwh)

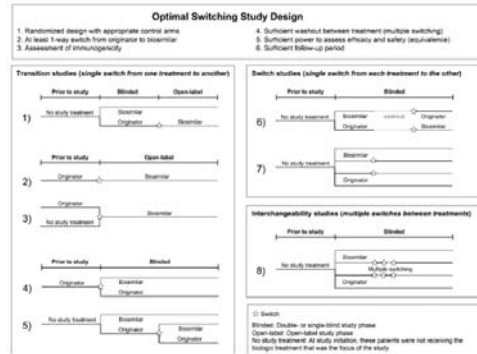
US FDA [website]. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>; Emicizumab-kxwh prescribing information [website]. [https://www.gene.com/download/pdf/hemlibra\\_prescribing.pdf](https://www.gene.com/download/pdf/hemlibra_prescribing.pdf). Accessed February 5, 2018. US FDA. Designation of official names and proper names for certain biological products. August 25, 2015. <https://www.fda.gov/oc/foia/2015/08-25-15-proposedrule.pdf?1520688960>. Accessed April 3, 2018.

### FDA Draft Guidance for Interchangeability

- Interchangeability: The biosimilar product is expected to produce the same clinical result as the reference product in any given patient
- Biosimilar sponsors should consult with FDA early on to discuss their plans to demonstrate interchangeability
- Sponsors should consider an array of factors when determining the type and amount of data to support a demonstration of interchangeability
  - Product complexity
  - Product-specific immunogenicity risk
- Sponsors should consider the “totality of factors” for their product to determine the amount and type of data that will be required to demonstrate interchangeability

Regulatory Affairs Professionals Society (RAPS) [website]. FDA issues long-awaited biosimilar interchangeability guidance. Michael Mezher. January 17, 2017. <https://www.raps.org/regulatory-focus/news-articles/2017/1/fda-issues-long-awaited-biosimilar-interchangeability-guidance>. Accessed April 2, 2018.

## Biosimilar Switching and Switch Trial Design



Moots R, et al. *Curr Rheumatol Rep.* 2017;19(6):37.

## Biosimilar Equivalence and Switching

### • The ABP 980 Phase 3 LILAC study

- Evaluated the safety and efficacy of the trastuzumab biosimilar ABP 980 compared to the reference product in patients with HER-2-positive breast cancer
- Primary endpoints: Risk difference (RD) and risk ratio (RR) of pathologic complete response in breast tissue and axillary lymph nodes (equivalence margins:  $\pm 13\%$  for RD, 0.759-1.318 for RR)
- Local review found 48% (ABP 980) and 40.5% (trastuzumab) of patients achieved pathologic complete response
- RD and RR of pathologic complete response were 7.3% (90% CI: 1.2, 13.4) and 1.19 (90% CI: 1.033, 1.366), respectively

### • Comparison of Switching from the Originator Rituximab (RTX) to the Biosimilar Rituximab GP2013 or Retreatment with the Originator RTX

- Safety and immunogenicity of the switch from RTX to GP2013 compared with continued RTX in patients with active RA
- Patients randomized (1:1) to receive 1000 mg of GP2013 (switch group, n=53) or continue RTX (control group, n=54) for 24 weeks
- Majority of patients completed the study; incidence of hypersensitivity, infusion-related reactions, and other adverse events were low and similar in both groups
- Safety profile of patients who switched from RTX to GP2013 was comparable with the patients who received continued treatment with RTX

Von Minckwitz G. Presented at: European Society for Medical Oncology (ESMO) 2017 Congress; September 9, 2017; Madrid, Spain. Abstract 151PD. Tony HP, et al. Presented at: The 2017 ASCO Annual Meeting; November 7, 2017; San Diego, California. Abstract 2795.

## State-Level Biosimilar Substitution Legislation Continues

- In the past 5 years, 48 states have considered legislation
- 38 states, plus Puerto Rico, have enacted laws
- Common features
  - FDA determination as interchangeable – "Purple Book"
  - Physician dispense as written authority
  - Physician notification, patient notification, and consent of substitution
  - Record-keeping requirements
  - Cost information to the patient
  - Immunity in some states for pharmacists who make a substitution in compliance with biologics state law

National Conference of State Legislatures [website]. <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>. Accessed April 2, 2018.

Change in Mindset

## European Crohn's and Colitis Foundation Position Statement (2013)

- "Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity."
- "A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective."
- "Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis."
- "Any decision to substitute a product should only be made with the prescribing health care provider's specific approval and patient knowledge."



Danese S, et al. *J Crohns Colitis*. 2013;7(7):586-589.

## European Crohn's and Colitis Foundation Position Statement (2017)

- "Biosimilarity is more sensitively characterized by performing suitable in vitro assays than clinical studies."
- "Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the use of biosimilars in IBD can be extrapolated from another sensitive indication."
- "When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics."
- "Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients."



Danese S, et al. *J Crohns Colitis*. 2017;11(1):26-34.

## Not All Mindsets Have Changed

- "Generally, FDA approval of a biosimilar product is an indication that safety and efficacy are not meaningfully different from the reference product."
  - **Not just a general assertion; it IS the definition of a biosimilar**
- "The FDA approval process for biosimilars makes it less likely that large, phase III trials will be undertaken for all approved indications of the reference product."
  - **Not just less likely; it is guaranteed NOT to occur**



Lyman GH, et al. *J Clin Oncol*. 2018 Apr 20;36(12):1260-1265.

## Understanding Biosimilar Value and Other Impossible Tasks



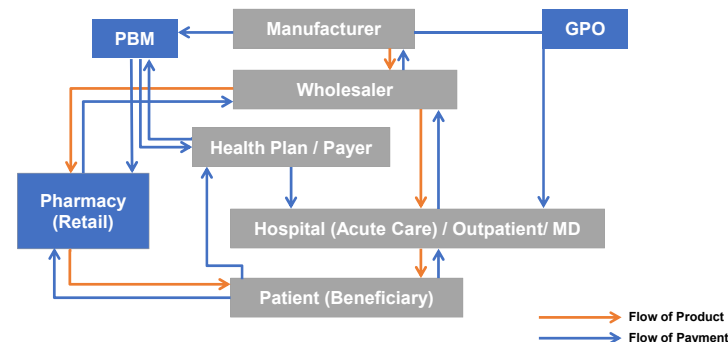
## Medicare Part B

- **Prior to January 1, 2018**
- Biosimilars had unique HCPCS code from originator
  - Filgrastim (biosimilar) = Q5101; infliximab (biosimilar) = Q5102
- However, biosimilars of the same originator shared HCPCS codes
  - 100% of biosimilar ASP x 6% ASP<sup>a</sup> of the originator
  - Must use 2-digit identifier to distinguish which biosimilar used
  - ZA = Novartis/Sandoz, ZB = Pfizer/Hospira, ZC = Merck/Samsung Bioepis
- **After January 1, 2018**
  - All biosimilars will be assigned unique HCPCS codes
  - All biosimilars are now eligible for "pass-through" payment; impact for 340B Disproportionate Share Hospitals

<sup>a</sup>4.3% due to sequestration.

HCPCS = Healthcare Common Procedure Coding System; ASP = average sales price. Centers for Medicare & Medicaid Services [website]. <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html>. Accessed February 5, 2018.

## The Dimensions of Payment (Medical and Pharmacy)



PBM = pharmacy benefit manager; GPO = group purchasing organization.

Academy of Managed Care Pharmacy (AMCP) Guide to Pharmaceutical Payment Methods. 2013 Update. Alexandria, VA: AMCP; 2013.

## What Savings Have We Seen?

### Filgrastim-sndz

- 15% initial discount (WAC)

### Tbo-filgrastim

- 19% discount (WAC)

### Infliximab-dyyb

- 15% of originator infliximab WAC

### Infliximab-abda

- 35% of originator infliximab WAC

WAC = wholesale acquisition cost.

Modern Healthcare [website]. <http://www.modernhealthcare.com/article/20160323/NEWS/160319919>. DrugCodeLookup [website]. <http://www.drugcodelookup.com>. Big Molecule Watch [website]. <http://www.bigmoleculewatch.com/2017/07/24/samsung-bioepis-and-merck-co-launch-renflexis-a-lower-priced-competitor-to-inflectra>. Accessed February 5, 2018.

## Are Coverage Levels Improving?

### Example (filgrastim-sndz)

- Cigna (Medical/Pharmacy) – 1 of 2 preferred
- CVS/Caremark (Medical/Pharmacy) – Exclusive
- ESI (Pharmacy) – 1 of 2 preferred
- Humana (Medical/Pharmacy) – 1 of 2 preferred
- Magellan (Medical) – Exclusive
- OptumRx (Pharmacy) – 1 of 3 preferred
- Prime Therapeutics (Pharmacy) – 1 of 2 preferred
- United (Pharmacy) – Exclusive

Data on file. Sandoz.

## Preparing for the Future

## Integrating Biosimilars into Clinical Plans

- Educate physicians and other healthcare providers, payers, and patients about biosimilars to:
  - Facilitate informed decision making
  - Promote acceptance of biosimilars into clinical practice
  - Increase accessibility
  - Expedite associated health and economic benefits
  - Increase their confidence
- Be aware of the nocebo effect (ie, the negative equivalent to the placebo effect)
  - Patients switched to/prescribed biosimilars (or even generics) have greater discontinuation rates due to perceived lack of efficacy and adverse effects
  - Providers can unintentionally influence patient perceptions and give patients a negative perception of biosimilars through choice of words and any perceived lack of confidence
- Discuss the importance of shared decision making

Rezk MR, et al. *Rheumatol Ther*. 2017;4:209-218. Jorgensen TS, et al. 2017 ACR/ARHP Annual Meeting. *Arthritis Rheumatol*. 2017;69(suppl10): Abstract 2260. Bridges SL, et al. *Arthritis Rheumatol*. 2018 Mar;70(3):334-344.

## Elements of a Formulary Review Document (Biosimilar Perspective)

- **Brand and generic names and synonyms**
- FDA approval information
- Pharmacology and mechanism of action
- FDA-approved indications
- Potential non-FDA-approved indications
- **Dosage form and storage**
- Recommended dosage regimens
- Pharmacokinetic considerations
- Use in special populations
- Pregnancy category and use during breast-feeding
- Comparisons of the drug's efficacy, safety, **convenience, and costs with those of therapeutic alternatives**
- Clinical trial analysis and critique
- Medication safety assessments and recommendations
  - Adverse drug reactions
  - Drug–drug, drug–food interactions
  - **Sound-alike and look-alike issues**
- **Financial analysis**

ASHP [website]. <https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/gdl-pharmacy-therapeutics-committee-formulary-system.ashx>. Accessed February 5, 2018.

## Biobetters and Beyond

Existing Agent	Modification
<b>Neulasta® (pegfilgrastim)</b>	• Pegfilgrastim on-body injector (Neulasta® Onpro®)
<b>Rituxan® (rituximab) intravenous injection</b>	• Rituximab subcutaneous • Obinutuzumab
<b>Herceptin (trastuzumab)</b>	• Trastuzumab 150 mg • Pertuzumab • Ado-trastuzumab emtansine
<b>Remicade (infliximab)</b>	• Guselkumab (IL-23 inhibitor for plaque psoriasis)
<b>Humira® (adalimumab)</b>	• ABT-122 (bispecific antibody for TNF/IL-17) • ABT-494 (Janus kinase-1 inhibitor) • ALX-0061 (anti-interleukin-6 receptor) mAb

US FDA [website]. Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed March 1, 2018.

## Summary

- The age of biosimilars has arrived (slowly)
- As we move later into 2018 and especially 2019, the rate of approval and launch of biosimilars should increase
- Failure to achieve meaningful uptake could greatly limit the degree of value biosimilars could bring to the market as incentives for more participants would decrease
- Robust uptake and acceptance would make subsequent adoption of future biosimilars (ie, immunotherapy biologics) less challenging
- Pharmacists must lead the way in addressing potential roadblocks (eg, clinical concerns, economic challenges, costs of conversion) to support appropriate evaluation and use of biosimilars

Questions?

## Examining the Pharmacologic Profiles and Appropriate Integration of Treatment Advances in AML



This session is supported by an educational grant from Jazz  
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## Disclosures

**Dr. Fausel** has disclosed no relevant financial relationships with any commercial interest.

## Learning Objectives

- Describe the factors that contribute to poor clinical outcomes and the economic burden of AML
- Identify the challenges with the current standard of AML care and traditional therapeutic options in terms of the initiation, tolerability, and toxicity of treatment; and impact on patient survival, hospitalizations, and quality of life
- Assess the role of novel chemotherapeutic formulations and targeted agents in the treatment of AML in terms of clinical outcomes, pharmacologic profiles, reduced toxicity, and pharmacoeconomic data
- Integrate new chemotherapeutic formulations and targeted agents into AML care and pharmacy medication management plans

AML = acute myeloid leukemia.

## AML Epidemiology

- Estimated cases for 2018: 19,250
- Estimated annual deaths: 10,670
  - Almost all are in adults
- Median age at diagnosis: 68 years
- 5-year survival rate (2007-2013): 27%

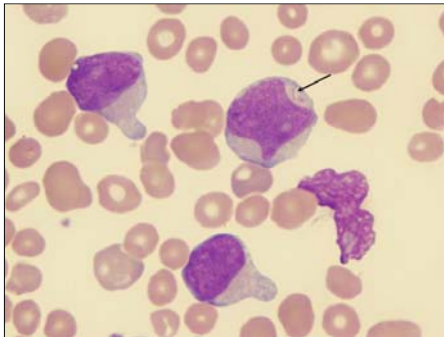
American Cancer Society [website]. Key statistics for AML. <https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html>. Accessed January 30, 2018. Howlader N, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. <https://seer.cancer.gov/statfacts/html/aml.html>. Accessed January 30, 2018.

## Diagnosis

- At least 20% of cells in peripheral blood or bone marrow are blasts that are myeloid in origin
- Exception includes t(15;17), t(8;21), inv(16), or t(16;16)
  - No blast limit

Vardiman JW, et al. *Blood*. 2009;114(5):937-951.

## AML Peripheral Blast Cells



University of Virginia Health System [website]. <http://www.healthsystem.virginia.edu/>. Accessed January 30, 2018.

## AML: Morphologic Classification (FAB Criteria)

Subtype	Description
M0	Undifferentiated; blast cells express myeloid antigens
M1	Acute myeloblastic leukemia with minimal differentiation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5a	Acute monoblastic leukemia without differentiation
M5b	Acute monoblastic leukemia with differentiation
M6	Acute erythroleukemia
M7	Megakaryocytic leukemia

FAB = French-American-British.  
Döhner H, et al. *N Engl J Med*. 2015;373(12):1136-1152.

## Risk Factors

- **Age**
  - 50% of people with AML are older than 65 years when diagnosed
- **Smoking**
  - Linked to tobacco smoke exposure
- **Certain chemical exposures**
  - Long-term exposure to products that contain benzene
- **Genetic disorders**
  - Occur more often in people with the following inherited disorders
    - Down syndrome
    - Ataxia telangiectasia
    - Li-Fraumeni syndrome
    - Klinefelter syndrome
    - Fanconi anemia
    - Wiskott-Aldrich syndrome
    - Bloom syndrome
    - Familial platelet disorder

American Cancer Society [website]. What are the risk factors for acute myeloid leukemia? <https://www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html>. Accessed May 30, 2017. Cancer.Net® [website]. American Society of Clinical Oncology (ASCO). 2017. Leukemia – acute myeloid – AML: risk factors. <http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/risk-factors>. Approved January 2016. Accessed May 30, 2017.

## Risk Factors (cont)

- **High doses of radiation**
  - People who have been exposed to high levels of radiation, such as long-term survivors of nuclear accidents
  - Electromagnetic fields generated by high-voltage electrical wires have not been shown to cause AML
- **Previous cancer chemotherapy**
  - People who have received chemotherapy and/or radiation therapy for other types of cancer, such as breast cancer, ovarian cancer, and lymphoma, have a higher risk of developing AML in the years following treatment
- **Other bone marrow disorders**
  - People who have other bone marrow diseases, including myeloproliferative disorders, can develop AML over time
  - Conditions include
    - Polycythemia vera
    - Myelofibrosis
    - Essential thrombocytosis
    - Myelodysplastic syndrome

American Cancer Society [website]. What are the risk factors for acute myeloid leukemia? <https://www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html>. Accessed May 30, 2017. Cancer.Net® [website]. American Society of Clinical Oncology (ASCO). 2017. Leukemia – acute myeloid – AML: risk factors. <http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/risk-factors>. Approved January 2016. Accessed May 30, 2017.

## AML: Signs and Symptoms

- **Clinical manifestations**
  - Bone marrow failure: Infection, bleeding, anemia
  - Extramedullary tissue invasion: Granulocytic sarcoma
  - Leukostasis secondary to high WBC count
  - Tumor cell breakdown: Dysregulation of electrolytes (eg, elevated potassium, phosphate, and uric acid; depressed calcium)
    - At risk for tumor lysis syndrome

WBC = white blood cell.  
Döhner H, et al. *N Engl J Med*. 2015;373:1136-1152.

## Impact of Cytogenetics/Genomics

Risk	Cytogenetic Abnormality	Molecular Mutation
<b>Favorable</b>	Inv(16) t(16;16) t(8;21) t(15;17)	Normal cytogenetics with <i>NPM1</i> mutation or isolated <i>CEBPA</i>
<b>Intermediate</b>	Normal cytogenetics +8 t(9;11)	Inv(16), t(16;16), t(8;21) with <i>c-KIT</i> mutation Mutated <i>NPM1</i> without <i>FLT3-ITD</i> Wild-type <i>NPM1</i> without <i>FLT3-ITD</i>
<b>Adverse</b>	Complex cytogenetics (>3 abnormalities) 11q23 Inversion 3 t(3;3), or t(6;9) or t(9;22)	Normal cytogenetics with <i>FLT3-ITD</i> mutation Wild-type <i>NPM1</i> and <i>FLT3-ITD</i> Mutated <i>RUNX1</i> , <i>ASXL1</i> , or <i>TP53</i>

ITD = internal tandem duplication.  
Döhner H, et al. *Blood*. 2017;129(4):424-447.

## AML Treatment Goals

Treatment Phase	Goal
<b>Induction</b>	Achieve a remission CR criteria Peripheral neutrophil count $>1.0 \times 10^9$ Platelet count $>100 \times 10^9$ Patient independent of transfusions Bone marrow $<5\%$ blasts Absence of blasts with Auer rods Absence of extramedullary disease
<b>Post-remission therapy (consolidation)</b>	Maintain remission and ultimately achieve cure

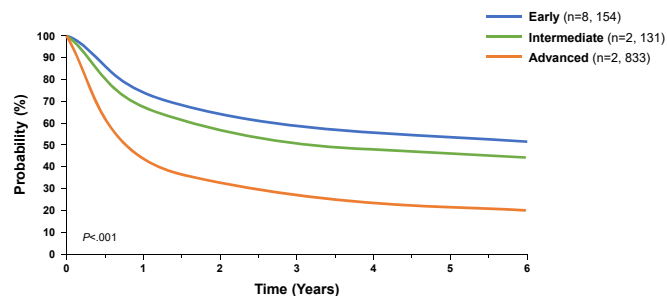
Döhner H, et al. *Blood*. 2010;115(3):453-474.

## General Approach to Treatment

Treatment Phase	Drug Therapy
<b>Induction</b>	Cytarabine 100-200 mg/m <sup>2</sup> IV continuous infusion daily x 7 days Daunorubicin 60-90 mg/m <sup>2</sup> IV daily on days 1, 2, and 3 (idarubicin 12 mg/m <sup>2</sup> IV could be substituted for daunorubicin on days 1, 2, and 3) **Bone marrow biopsy conducted at 10-14 days; if residual leukemia, then repeat induction
<b>Consolidation</b>	Cytarabine 3000 mg/m <sup>2</sup> IV Q12H on days 1, 3, and 5 – generally x 4 cycles OR Autologous or allogeneic SCT
<b>Relapse</b>	Reinduction chemotherapy (eg, MEC – mitoxantrone, etoposide cytarabine) Allogeneic SCT Palliative care

IV = intravenous; Q12H = every 12 hours; SCT = stem cell transplantation.  
Döhner H, et al. *Blood*. 2017;129(4):424-447.

## Allogeneic SCT for AML



Center for International Blood and Marrow Transplant Research [website]. <https://www.cibmtr.org/Pages/index.aspx>. Accessed February 5, 2018.

## Challenges with Traditional Standard of Care with 7+3 Therapy

- 7+3 therapy: 7 days of continuous infusion-dose cytarabine and 3 days of anthracycline, most commonly daunorubicin
  - Typically administered in the inpatient setting
  - Side effects
  - Hospitalizations
  - Complex regimen may increase risk of medication error
- Difficult-to-treat populations
  - Elderly (undertreatment of “healthy” elderly and managing elderly in poor health)
  - Comorbidities
  - Cannot tolerate standard intensive therapy or contraindicated
  - Complex cytogenetics

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia. Version 1.2017. February 24, 2017. [www.nccn.org/professionals/physician\\_gls/pdf/aml.pdf](http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed December 14, 2017. Nazha A, et al. *Leuk Lymphoma*. 2014;55(5):979-987. Sasine JP, et al. *Blood Rev*. 2015;29:1-9. Meyers J, et al. *Appl Health Econ Health Policy*. 2013;11:275-286.

## Need for New Regimens and Targeted Agents

## NCCN® AML Guideline Updates

- February 8, 2018: National Comprehensive Cancer Network (NCCN®) adds daunorubicin/cytarabine liposome for injection to the Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML
- NCCN Guidelines now include a Category 1 recommendation\* for use of daunorubicin/cytarabine liposome for adult patients aged 60 years and older with newly diagnosed t-AML or AML-MRC
- Multiple regimens were added to the preferred section of the treatment induction for high-risk disease recommendations
- Relapsed or refractory disease, a sub-section for clinical trials, was added
- Categories for therapy for AML with IDH2 mutation and therapy for CD33-positive AML were added
- Enasidenib was added as a regimen to AML with IDH2 mutation
- Gemtuzumab ozogamicin was added as a regimen to CD33-positive AML

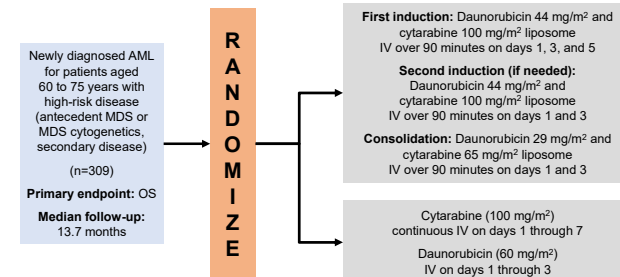
\*Category 1 recommendation indicates there is uniform NCCN consensus that daunorubicin/cytarabine liposome is appropriate for these patients based on high-level evidence.  
 NCCN = National Comprehensive Cancer Network; t-AML = therapy-related AML; MRC = myelodysplasia-related changes; IDH2 = isocitrate dehydrogenase-2.  
 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia. Version 1.2017. February 24, 2017. [www.nccn.org/professionals/physician\\_gls/pdf/aml.pdf](http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed February 15, 2018. Journal of Clinical Pathways [website]. NCCN issues extensive updates to acute myeloid leukemia guideline. February 9, 2018. <https://www.journalofclinicalpathways.com/news/nccn-issues-extensive-updates-acute-myeloid-leukemia-guideline>. Accessed February 21, 2018.

## Daunorubicin/Cytarabine Liposome (CPX-351)

<b>FDA Approval</b>	August 3, 2017
<b>FDA-labeled indication</b>	Treatment of adult patients with newly diagnosed t-AML or AML with MRC
<b>Pharmacology</b>	Combination of anthracycline–DNA intercalation and polymerase inhibition/topoisomerase II inhibitor, and cytarabine (antimetabolite) in 5:1 molar ratio encapsulated in liposomes
<b>Dosing</b>	<p><b>First induction:</b> Daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> liposome IV over 90 minutes on days 1, 3, and 5</p> <p><b>Second induction (if needed):</b> Daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> liposome IV over 90 minutes on days 1 and 3</p> <p><b>Consolidation:</b> Daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> liposome IV over 90 minutes on days 1 and 3</p>

FDA = US Food and Drug Administration.  
 FDA [website]. Approved drugs. <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm569950.htm>. Accessed February 5, 2018.

## Daunorubicin/Cytarabine Liposome (CPX-351)



MDS = myelodysplastic syndrome; OS = overall survival.  
 Lancet JE, et al. *Proc Am Soc Clin Oncol*. 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.



## Efficacy Results

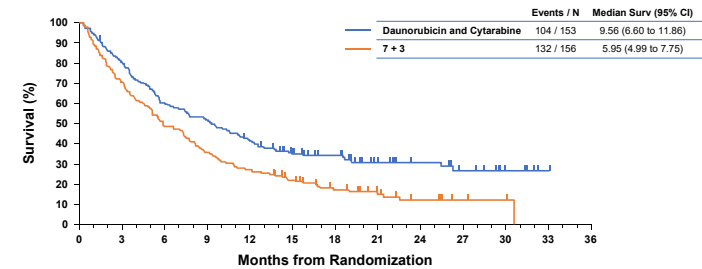
Parameter	CPX-351 (n=153)	Standard Cytarabine + Daunorubicin (n=156)
Median OS	9.6 months	5.9 months
EFS	HR=0.74 (P=.021)	
CR	38%	26%
All-cause 30-day mortality	6%	11%
60-day mortality	14%	21%

\*Similar numbers of patients received SCT in each arm.

EFS = event-free survival; CR = complete remission; HR = hazard ratio.

Lancet JE, et al. *Proc Am Soc Clin Oncol*. 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

## Kaplan-Meier OS Curve



Daunorubicin and Cytarabine	153	122	92	79	62	46	34	21	16	11	5	1
7 + 3	156	110	77	56	43	31	20	12	7	3	2	0

CI = confidence interval.

Lancet JE, et al. *Proc Am Soc Clin Oncol*. 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

## Toxicity (≥ Grade III)

Parameter	CPX-351 (n=153)	Standard Daunorubicin and Cytarabine (n=151)
Hemorrhage	10%	6%
Febrile neutropenia	66%	68%
Bacteremia (excluding sepsis)	23%	21%
Pneumonia (excluding fungal)	20%	17%
Hypoxia	12%	15%
Dyspnea	11%	10%
Non-conduction cardiotoxicity	9%	10%
Fungal infection	7%	6%
Diarrhea/colitis	3%	7%
Delirium	3%	6%
Renal insufficiency	5%	5%

Lancet JE, et al. *Proc Am Soc Clin Oncol*. 2016. Abstract 7000. Seiter K, et al. Medscape [website]. AML treatment protocols. Last updated October 12, 2017. Accessed February 5, 2018.

## CPX-351 Outcomes Summary

- CPX-351 improved outcomes in newly diagnosed, high-risk AML and t-AML
- 53% fewer deaths within 100 days of patients receiving transplantation following a response from induction therapy vs those who received 7+3 regimen
- Long-term analysis: More patients lived longer after transplantation vs those treated with standard 7+3 regimen

Castellino AM. CPX-351: Better Outcomes in Older High-Risk AML Patients. December 14, 2016. [www.medscape.com/viewarticle/873267](http://www.medscape.com/viewarticle/873267). Accessed December 14, 2017. Lancet JE, et al. *J Clin Oncol*. 2017;35(15 suppl):7035-7035. Medeiros BC, et al. *J Clin Oncol*. 2017;35:5.

## Midostaurin

**FDA Approval** April 28, 2017

**FDA-labeled indication** Treatment of adult patients with newly diagnosed AML that is FLT3 mutation positive detected by an FDA-approved test in combination with standard cytarabine and daunorubicin and cytarabine consolidation

**Pharmacology**

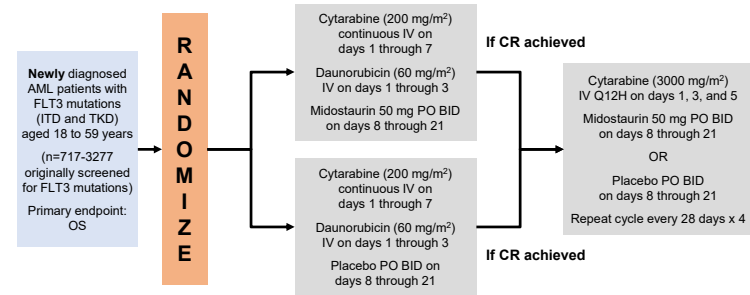
- Tyrosine kinase inhibitor of multiple kinases, including FLT3 – including mutant kinases ITD and KIT
- Inhibits FLT3 mediated receptor signaling and cell proliferation in leukemic cells

**Dosing**

**First Induction:** 50 mg PO BID with food on days 8 through 21  
**Consolidation:** 50 mg PO BID with food on days 8 through 21  
**\*Maintenance:** Midostaurin 50 mg PO BID or placebo every 28 days x 12

\*Not part of the FDA-labeled dosing.  
 PO = to take orally; BID = twice daily.  
 FDA [website]. Approved drugs. <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555756.htm>. Accessed February 5, 2018.

## Midostaurin in *FLT3* AML



\*Maintenance: Midostaurin 50 mg PO BID or placebo every 28 days x 12.

Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

## Efficacy Results

Parameter	Midostaurin (n=355)	Placebo (n=354)
Median OS	74.7 months	25.6 months
4-year OS	51.4%	44.3%
Median EFS	8.2 months	3 months
4-year EFS	28.2%	20.6%
Median disease-free survival	26.7 months	15.5 months
SCT performed in first remission (57% of all patients received SCT at some point)	28.1%	22.7%
Protocol-specified CR	59%	54%
Median time to CR	35 days	35 days

Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

## Toxicity (≥ Grade III)

Event	Midostaurin (n=355)	Placebo (n=354)
Neutropenia	95%	96%
Leukopenia	26%	30%
Thrombocytopenia	97%	97%
Anemia	93%	88%
Lymphopenia	19%	22%
Infections	52%	50%
Febrile neutropenia	82%	82%
Diarrhea	16%	15%
Hypokalemia	14%	17%
Rash	14%	8%
Fatigue	9%	10%
Pneumonitis/infiltrates	8%	8%

Stone RM, et al. *New Engl J Med*. 2017;377:454-464.

## Gemtuzumab Ozogamicin

**FDA Approval** September 1, 2017

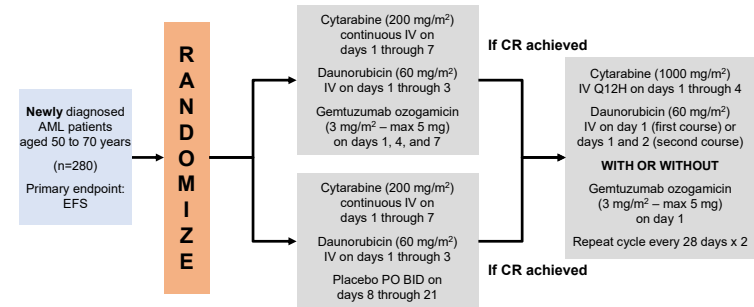
**FDA-labeled indication** Treatment of adult patients with newly diagnosed CD33+ AML or relapsed/refractory CD33+ AML in adults and pediatric patients 2 years and older

**Pharmacology** Antibody-drug conjugate with the antibody portion (gemtuzumab) binding to CD33 on AML blast cells and calicheamicin inducing double-strand DNA breaks when released from the linkage to the antibody intracellularly

**Dosing**  
**Induction:** 3 mg/m<sup>2</sup> IV on days 1, 4, and 7 in combination with daunorubicin and cytarabine or 6 mg/m<sup>2</sup> IV on day 1 and 3 mg/m<sup>2</sup> IV on day 8 when given as a single agent  
**Consolidation:** 3 mg/m<sup>2</sup> (max 4.5 mg) IV on day 1 with daunorubicin and cytarabine or 2 mg/m<sup>2</sup> IV on day 1 every 4 weeks following single-agent induction  
**Relapsed disease:** 3 mg/m<sup>2</sup> IV on days 1, 4, and 7

FDA [website]. Approved drugs. <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574518.htm>. Accessed February 5, 2018.

## Gemtuzumab Ozogamicin: Front Line



Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

## Efficacy Results

Parameter	Gemtuzumab Ozogamicin (n=139)	Standard Chemotherapy (n=139)
EFS	15.6 months	9.7 months
EFS at 24 months	41%	17%
Median OS	34 months	19 months
OS at 24 months	53%	42%
CR	81%	75%
Relapse	35%	44%
Relapse-free survival	28 months	11 months
Resistant disease	12%	21%

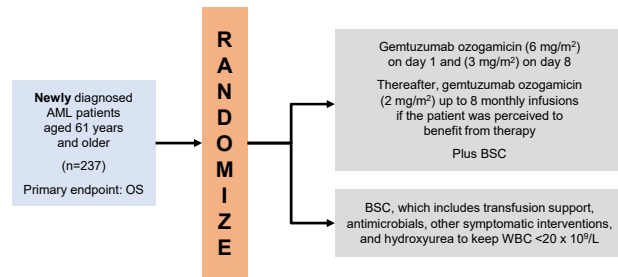
Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

## Toxicity (≥ Grade III)

Event	Gemtuzumab Ozogamicin (n=139)	Standard Chemotherapy (n=139)
<b>Neutropenia (&lt;500 mm<sup>3</sup>)</b>		
• Post induction	22 days	22 days
• Post 1st consolidation	13 days	10 days
• Post 2nd consolidation	15 days	13 days
<b>Thrombocytopenia</b>		
• Post induction	25 days	21 days
• Post 1st consolidation	17 days	9 days
• Post 2nd consolidation	24 days	13 days
<b>Induction deaths</b>	6%	4%
<b>Transfer to intensive care unit</b>	14%	12%
<b>Infection</b>	47%	41%
<b>Hemorrhage</b>	9%	3%
<b>Cardiac</b>	3%	4%
<b>Hepatic</b>	13%	6%

Castaigne S, et al. *Lancet*. 2012;379(9825):1508-1516.

## Gemtuzumab Ozogamicin: Single Agent



BSC = best-supportive care.  
Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

## Efficacy Results

Parameter	Gemtuzumab Ozogamicin (n=118)	BSC (n=119)
Median OS	4.9 months	3.6 months
6-month OS	46%	29%
12-month OS	24%	10%
All-cause 30-day mortality	11%	14%
CR + CRI (induction)	24%	N/A
CR + Cri (best response)	27%	N/A
Progressive disease	14%	N/A
Induction death	7%	N/A

Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

## Toxicity (≥ Grade III)

Parameter	Gemtuzumab Ozogamicin (n=119)	BSC (n=118)
Infection	35%	34%
Febrile neutropenia	18%	24%
Bleeding	13%	12%
Fatigue	12%	21%
Liver	7%	6%
Cardiac	6%	16%
Metabolic	4%	6%
Renal	4%	4%
Death due to any adverse effect	17%	20%

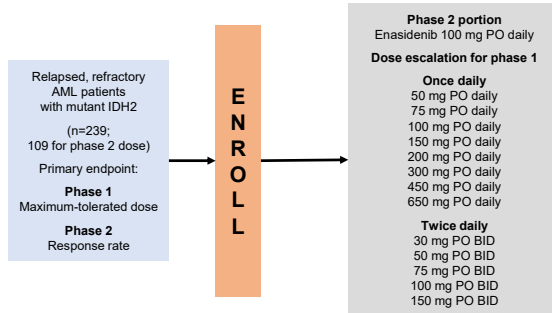
Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

## Enasidenib

FDA Approval	August 1, 2017
FDA-labeled indication	IDH2 inhibitor indicated for the treatment of adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test
Pharmacology	Small-molecule inhibitor of the IDH2 enzyme. Targets the mutant IDH2 variants R140Q, R172S, and R172K leading to decreased 2-HG levels, thereby inducing myeloid differentiation with a net result of reduced blast counts and increased percentages of mature myeloid cells
Dosing	100 mg PO daily until disease progression or unacceptable toxicity – with or without food

2-HG = 2-hydroxyglutarate.  
FDA [website]. Approved drugs. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm569482.htm>. Accessed February 5, 2018.

## Enasidenib



Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209606orig1s000toc.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm). Accessed February 5, 2018.

## Efficacy Results

Parameter	Enasidenib 100 mg Daily (n=109)	Enasidenib (All Doses) (n=176)
Overall response rate	38%	40%
CR	20%	19%
CRi	6%	7%
PR	3%	6%
Morphologic leukemia-free state	9%	8%
Stable disease	53%	48%
Progressive disease	5%	5%
Median time to first response	1.9 months	1.9 months
Median duration of response	5.6 months	5.8 months

Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209606orig1s000toc.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm). Accessed February 5, 2018.

## Toxicity (≥ Grade III)

Parameter	Enasidenib 100 mg Daily (n=153)	Enasidenib (All Doses) (n=239)
Hyperbilirubinemia	8%	12%
IDH differentiation syndrome	7%	6%
Anemia	7%	5%
Thrombocytopenia	5%	6%
Tumor lysis syndrome	3%	3%
Decreased appetite	2%	3%
Leukocytosis	1%	3%
Fatigue	1%	3%
Nausea	1%	2%
Lipase increased	1%	2%

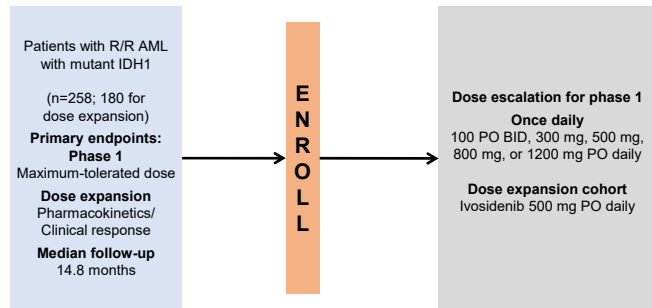
Stein EM, et al. *Blood*. 2017;130(6):722-731. FDA [website]. Approved drugs. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209606orig1s000toc.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209606orig1s000toc.cfm). Accessed February 5, 2018.

## Ivosidenib

FDA Approval	July 20, 2018
FDA-labeled indication	Adult patients with relapsed/refractory AML with a susceptible IDH1 mutation detected by an FDA-approved test
Pharmacology	<ul style="list-style-type: none"> <li>Small-molecule inhibitor of the IDH1 enzyme</li> <li>Targets the mutant IDH1 variant R132 leading to decreased 2-HG levels, thereby inducing myeloid differentiation with a net result of reduced blast counts and increased percentages of mature myeloid cells</li> </ul>
Dosing	500 mg PO daily

IDH1 = isocitrate dehydrogenase-1; 2-HG = 2-hydroxyglutarate.  
FDA [website]. Approved drugs. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm614128.htm>. Accessed September 5, 2018.

## Ivosidenib (AG-120) Phase 1 and Dose Expansion



DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

## Toxicity (≥ Grade III)

Event	R/R AML with 500 mg/d (n=179)	Overall Population (n=258)
≥1 treatment-related event ≥ grade III	21%	26%
Prolongation of QT interval on ECG	8%	7%
IDH differentiation syndrome	4%	5%
Anemia	2%	2%
Thrombocytopenia	2%	2%
Leukocytosis	2%	1%
Febrile neutropenia	1%	1%
Diarrhea	1%	1%
Platelet count decreased	3%	1%
Hypoxia	1%	1%

DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

## Efficacy Results

Parameter	Primary Efficacy Population (n=125)	Relapsed or Refractory AML (n=179)
CR or CRh	30%	30%
Overall RR	42%	39%
Median duration of response	6.5 months	NR
Median time to response	1.9 months	NR
Median overall survival	8.8 months	NR
18-month survival	50%	NR
Transfusion independence*	35% for 56 days or more	NR

\*Based on 84 patients who required transfusions.  
NR = not reported.  
DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

## Economic Burden of AML

- **Cost drivers**
  - Hospital reimbursement
  - Physician payments
  - Outpatient hospital payments
  - Home healthcare payments
- **Indirect costs**
  - Caregiver burden
  - Transportation costs
  - Time spent in hospital
  - Home care

Menzin J, et al. *Arch Intern Med.* 2002;162(14):1597-1603. Leunis A, et al. *Leuk Res.* 2013;37(3):245-250. Vaughn JE, et al. *JAMA Oncol.* 2015;1(8):1120-1127. Meyers J, et al. *Value Health.* 2012;15(4):A214. Walter RB, et al. *Clin Adv Hematol Oncol.* 2013;11(9):571-577.

## Economic Burden of AML (cont)

- Average direct costs/patient vary widely: \$14,000 (BSC) to \$353,700 (allogeneic SCT)
- Average direct costs (2012)
  - Induction of remission (1 cycle): \$56,802
  - Consolidation (2 cycles): \$113,176
- Healthcare costs among patients with AML are primarily driven by inpatient care

Bahmoud D, et al. *Blood*. 2012;120:3614. Zeidan AM, et al. *Exp Rev Hematol*. 2016;9(1):79-89. Leunis A, et al. *Leuk Res*. 2013;37(3):245-250. Vaughn JE, et al. *JAMA Oncol*. 2015;1(8):1120-1127. Meyers J, et al. *Value Health*. 2012;15(4):A214. Walter RB, et al. *Clin Adv Hematol Oncol*. 2013;11(9):571-577.

## Drug Acquisition Costs

Drug	Cost
Cytarabine 100 mg	\$19.81
Daunorubicin 20 mg	\$125.40
Daunorubicin/cytarabine liposome (CPX-351) 44 mg/100 mg	\$7750.00
Midostaurin 25 mg (#112)	\$15,889.00
Gemtuzumab ozogamicin 4.5 mg	\$8200.00
Enasidenib 100 mg (#30)	\$24,872.00

Grosse SD, et al. *Thromb Res*. 2016;137:3-10. The University of Utah [website]. Research profiles. Indiana University Health Department of Pharmacy, January 30, 2018.

## Cost-Effectiveness of CPX-351 vs 7+3 Regimen based on Health Economic Model

- Phase 3 trial in elderly patients with newly diagnosed t-AML or AML-MRC
- Superior OS (9.56 vs 5.95 months) and improved CR rate (38% vs 26%) with CPX-351 vs 7+3 regimen
- Results
  - Treatment with CPX-351 projected to provide an additional 1.9 years of life vs 7+3 regimen
  - Costs and improved clinical outcomes yield an incremental cost-effectiveness ratio of \$111,385/QALY gained over 7+3 regimen
  - Favorable balance between clinical gains and incremental costs of treatment
  - CPX-351 is a cost-effective option in treatment of patients with t-AML or AML-MRC

Kansal A, et al. *Blood*. 2017;130:4674. Lancet J, et al. *J Manag Care Spec Pharm*. 2016;22:4-a:S39.

## Summary: Pharmacoeconomics

- Cost of treatment is only one consideration
- Other factors to consider
  - Reduced hospitalizations
  - Improved SE profiles
  - Treatment simplicity to reduce medication errors
  - Genomic testing/targeted agents to reduce inappropriate use of ineffective treatment
  - Newer agents with improved efficacy and tolerability, which may help reduce hospitalizations

Grosse SD, et al. *Thromb Res*. 2016;137:3-10. The University of Utah [website]. Research profiles. Indiana University Health Department of Pharmacy, January 30, 2018.

## Emerging Agents

- **Crenolanib:** Phase 2 trials showed positive results; phase 3 trials currently being planned
- **Elacetytarabine:** Phase 3 development; received orphan drug designation from FDA and European Medicines Agency; received fast track designation from FDA
- **Gilteritinib:** Phase 3 clinical trials; received orphan drug status and fast track designation from FDA in 2017
- **Quizartinib:** Phase 3 clinical trials (QUANTUM-R studies); granted orphan drug designation from FDA and European Commission in 2015
- **Sapacitabine:** Phase 3 clinical trial (SEAMLESS); alternating schedule with decitabine
- **Sorafenib:** Studied in combination with cytotoxic agents (eg, crenolanib)
- **Vosaroxin:** Phase 3 clinical trials (VALOR)

Fathi AT, et al. *Eur J Haematol.* 2017;98:330-336. Saygin C, et al. *J Hematol Oncol.* 2017;10:93. Kuznar W. OncLive [website]. New AML drugs approved and under investigation in 2017. October 9, 2017. Accessed February 15, 2018. GEN News Highlights. Cyclacel Phase III Sapacitabine AML Study Fails to Meet Primary Endpoint. February 23, 2017. [www.genengnews.com/gen-news-highlights/cyclacel-phase-iii-sapacitabine-aml-study-fails-to-meet-primary-endpoint/61253923](http://www.genengnews.com/gen-news-highlights/cyclacel-phase-iii-sapacitabine-aml-study-fails-to-meet-primary-endpoint/61253923). Accessed February 15, 2018. Specialist Pharmacy Service [website]. [www.sps.nhs.uk](http://www.sps.nhs.uk). Accessed February 21, 2018.

## Role of the Pharmacist

- AML involves a highly specialized patient population
- Supportive care is critical to the survival of these patients, particularly during the induction phase when patients are aplastic for weeks
  - Antibiotics, antifungal, transfusion support
- Risks of bleeding and infection inform all drug-therapy decision making
- Specific training and expertise required
  - Hematology/oncology, infectious diseases, general internal medicine, critical care

Pedersen CA, et al. *Am J Health Sys Pharm.* 2011;68(8):669-688. Gamble KH. Pharmacists' influence growing in hospitals. *Pharmacy Times.* May 31, 2011.

## Role of the Pharmacist (cont)

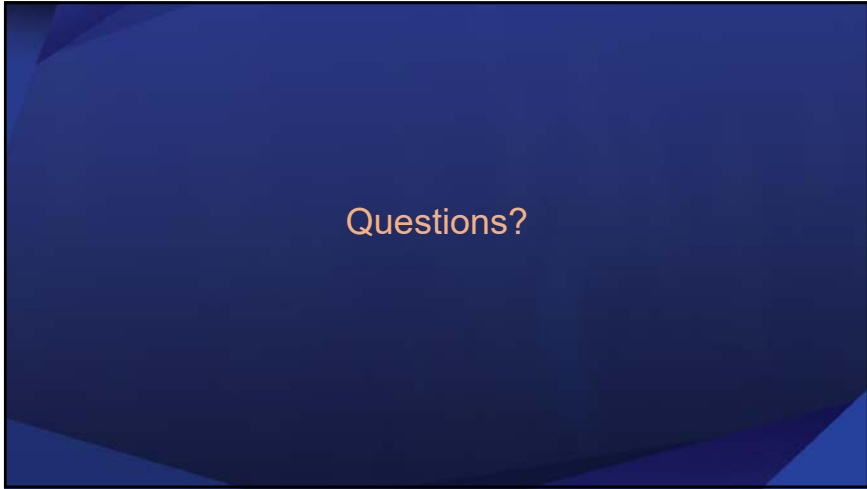
- Reduce medication errors by recommending newer, simplified chemotherapeutic regimens
- Ensure genomic/biomarker testing and recommend therapies that target specific genetic factors to avoid ineffective treatments
- Monitor/mitigate AEs
- Provide patient education on SE potential, treatment regimens, etc
- Educate the clinical team on new and emerging therapies

Pedersen CA, et al. *Am J Health Sys Pharm.* 2011;68(8):669-688. Gamble KH. Pharmacists' influence growing in hospitals. *Pharmacy Times.* May 31, 2011.

## Conclusions

- After decades of disappointing clinical research results, the approval of 4 new agents in 2017 has sparked a new wave of interest in the treatment of AML
  - Daunorubicin/cytarabine liposome, gemtuzumab ozogamicin, enasidenib, and midostaurin have generated modest but meaningful improvements in clinical outcomes for patients with AML
  - These new agents require the expertise of pharmacists on the care team to ensure proper education for patients and provision of appropriate supportive care





Questions?

## The Pharmacist's Role in Preventing Harm with Oral Anticoagulants



CELEBRATING  
10  
YEARS

### Faculty

**Matthew Grissinger, RPh, FISMP, FASCP**

Director, Error Reporting Programs  
Institute for Safe Medication Practices

Manager, Medication Safety Analysis  
PA Patient Safety Authority

### Disclosures

**Dr. Grissinger:** Employee (Spouse) – Johnson and Johnson

### Learning Objectives

- Describe errors and potentially hazardous situations associated with oral anticoagulants
- Evaluate the current trends in errors with the use of the newer oral anticoagulants
- Outline strategies for preventing anticoagulation errors using technology and other system changes
- Describe metrics that could be used to measure the level of patient harm with the use of oral anticoagulants

## History of Harm with Oral Anticoagulants

- One of the most commonly implicated drug classes in adverse drug events
- Most commonly implicated adverse drug events treated in US emergency departments and was responsible for 8% of all events
- Joint Commission NPSG 03.05.01 established 2008
- Retrospective, hospital-specific, 5-year study found that 48.8% (n=226) of all anticoagulant-associated adverse drug events involved medication errors

Office of Inspector General (OIG), US Department of Health and Human Services [website]. <http://oig.hhs.gov/oel/reports/oel-06-09-00090.pdf>. Accessed February 6, 2018. Budnitz DS, et al. JAMA. 2006;296:1858-1866. Joint Commission [website]. [https://www.jointcommission.org/assets/1/6/NPSG\\_Chapter\\_HAP\\_Jan2017.pdf](https://www.jointcommission.org/assets/1/6/NPSG_Chapter_HAP_Jan2017.pdf). Accessed February 6, 2018. Piazza G, et al. Am J Med. 2011;124(12):1136-1342.

## Ten Key Elements of Medication Use System

1. Patient information
2. Drug information
3. Communication of drug information
4. Labeling, packaging, and nomenclature
5. Drug storage, stock, standardization, and distribution
6. Device, acquisition, use, and monitoring
7. Environmental factors
8. Staff competency and education
9. Patient education
10. Quality and risk management issues

Institute for Safe Medication Practices [website]. [www.ismp.org/faq.asp#Question\\_3](http://www.ismp.org/faq.asp#Question_3). Accessed February 6, 2018.

## Patient Information

- **Lack of critical patient information**
  - Laboratory values
  - Weight
  - Diagnoses
  - Allergies
  - Other drug therapy
  - Order entry systems that do not use relevant patient information

## Patient Information Problems

- **Renal impairment**
  - Failure to reduce dose in patients with decreased renal function
- **Laboratory values**
  - Failure to verify laboratory values before prescribing or administering
  - Too frequent dose adjustments without assessing upward or downward trend in INR values

INR = international normalized ratio.

## Patient Information Problems

- **Duplicate or concurrent therapy**

- LMWH given in ED and heparin infusion started too soon on inpatient care unit
- Concomitant use of warfarin and other antithrombotics

- **Patient weight**

- Estimated or not verified
- Mix-ups between pounds and kilograms

ED = emergency department; LMWH = low-molecular-weight heparin.

## Medication Errors Associated with Wrong Patient Weights

Top Medications Involved in Wrong-Weight Medication Error Reports (n=304)

Medication	Total
Heparin sodium*	110
Enoxaparin (Lovenox®)*	84
Acetaminophen (Tylenol®)	20
Dobutamine*	17
Dopamine*	17
Gentamicin sulfate	17
Vancomycin	14
Ibuprofen (Motrin®)	9
Nesiritide (Natrecor®)	8
Propofol (Diprivan®)*	8

\*High-alert medications.  
Pennsylvania Patient Safety Authority [website]. [http://patientsafety.pa.gov/ADVISORIES/Pages/200903\\_10.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/200903_10.aspx). Accessed February 6, 2018.

## Medication Errors Associated with Wrong Patient Weights

Types of Errors Involving Wrong Weight (n=479)

Categories	Total	% of Total Reports
Confusion between pounds vs kilograms	129	26.9
Documented weight was too high	83	17.3
Documented weight was too low	48	10
No weight was available or used	45	9.4
Incorrect estimated weight	17	3.5
Mix-up between ideal vs actual weight	11	2.3
Calculation error	6	1.3
Mix-up between height/temperature vs weight	4	0.8
Others	10	2.1
Unknown*	126	26.3

\*There was not enough information mentioned in the report to determine what went wrong.  
Pennsylvania Patient Safety Authority [website]. [http://patientsafety.pa.gov/ADVISORIES/Pages/200903\\_10.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/200903_10.aspx). Accessed February 6, 2018.

## Communication of Drug Information Involving Oral Anticoagulants

- Confusing directions (alternate-day dosing)
- Changes in directions via telephone, which cause confusion for patients
- Failure to take recent prescribing of vitamin K into consideration when resuming therapy
- Automatic stop orders
- Failure to hold pre-procedure
- Failure to resume orders post-procedure
- Confusion with name

## Faxed Order for...

~~Heparin~~  
 Heparin 18000U  
 LU 180 CPWAS214 SQ 0.5 mL  
 Syringes 1cc 30 g/1 x 5  
 100

Institute for Safe Medication Practices [website]. <https://www.ismp.org/newsletters/acutecare/issue.aspx?id=20>. Accessed February 6, 2018.

## Dalteparin, Not Heparin

NOM NAME \_\_\_\_\_  
~~Heparin~~  
 → dalteparin 18000U  
 LU 180 CPWAS214 SQ 0.5 mL  
 30 g/1 x 5

Institute for Safe Medication Practices [website]. <https://www.ismp.org/newsletters/acutecare/issue.aspx?id=20>. Accessed February 6, 2018.

1 ~~D. warrenia~~ to 8 mg  
 PO daily

2 ~~Cecilia~~ Drug  
 disp: #90  
 Reg: PO daily

3 All previous cordura orders  
cordura 2 mg p.o. b.i.d.  
cordura 4 mg p.o. 2 am

## REVIEWS & ANALYSIS

### Oral Anticoagulants: A Review of Common Errors and Risk Reduction Strategies

Joseph A. Anderson, MD, PhD  
 Medical Director, PA, PhD, FACP  
 Manager, Patient Safety, American  
 Association of Colleges of Podiatric Medicine

#### ABSTRACT

Oral anticoagulants, a class of high-alert medications, are widely used in the United States for various indications, including treatment of acute or subacute thrombotic or pulmonary embolism as well as prevention of stroke in atrial fibrillation. Analysis of adverse medication events reported from July 2013 through June 2014 through the National Patient Safety Reporting System (NPSRS) involving four oral anticoagulants—warfarin, dabigatran, rivaroxaban, and apixiban. Of the 421 events related to oral anticoagulants, 32 (8%) were related to warfarin, 10 (2%) to dabigatran, 10 (2%) to rivaroxaban, and 10 (2%) to apixiban. The most common errors were related to warfarin (32, 8%), dabigatran (10, 2%), rivaroxaban (10, 2%), and apixiban (10, 2%). The most common errors were related to warfarin (32, 8%), dabigatran (10, 2%), rivaroxaban (10, 2%), and apixiban (10, 2%). The most common errors were related to warfarin (32, 8%), dabigatran (10, 2%), rivaroxaban (10, 2%), and apixiban (10, 2%).

Corresponding Author  
 Joseph A. Anderson

INTRODUCTION  
 Oral anticoagulants have been identified as one of the most commonly implicated drug classes in adverse drug events.<sup>1</sup> In fact, anticoagulation and cardiovascular agents, when compared with other medications, are more likely to cause potentially preventable adverse events due to medication errors.<sup>2</sup>

The Institute for Safe Medication Practices (ISMP) monitors and categorizes medication errors, and has been a long-standing advocate for the use of anticoagulants, such as dabigatran or rivaroxaban, to reduce the risk of bleeding events during treatment of acute and subacute thrombotic or pulmonary embolism.<sup>3</sup> The Institute for Safe Medication Practices (ISMP) has been a long-standing advocate for the use of anticoagulants, such as dabigatran or rivaroxaban, to reduce the risk of bleeding events during treatment of acute and subacute thrombotic or pulmonary embolism.

In a retrospective, longitudinal, 6-year study by Fries et al.,<sup>4</sup> the investigators found that 40.9% to 100% of all adverse drug events involved anticoagulation medication errors.<sup>4</sup> In the study, the 30-day mortality rate was increased in the 12% of patients who experienced an anticoagulation-related adverse drug event. Anticoagulation medication errors were the most common type of adverse drug event.

Four oral anticoagulants are approved and labeled for use for all of the acute indications. Warfarin, a vitamin K antagonist, works by altering the synthesis of vitamin C and E and is used in doses of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100.

Unlike warfarin, rivaroxaban and dabigatran cannot be monitored using standard coagulation tests (INR) or other blood tests and do not require dietary modifications.<sup>5</sup> Although all rivaroxaban and dabigatran are shown to be safe and

Andreica I, et al.  
 Pa Patient Saf Advis. 2015;12(2):54-61.

## Most Common Types of Events

Number of Oral-Anticoagulant-Related Medical Errors, by Event Type,  
Reported to the Pennsylvania Patient Safety Authority, July 2013 through June 2014 (N=831)

Event Type	n	%
Dose omission	270	32.5
Other (specify)	154	18.5
Extra dose	97	11.7
Wrong dose/overdosage	50	6.0
Monitoring error: clinical (lab value, vital sign)	46	5.5
Wrong time	40	4.8
Unauthorized drug	34	4.1
Wrong dose/underdosage	28	3.4
Wrong patient	23	2.8
Medication list incorrect	22	2.6

Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

## Errors with Oral Anticoagulants

- Medical-surgical units had the highest incidence of **reported** errors at 24.1% (n=200), followed by telemetry at 9.9% (n=82), and then rehabilitation units with 9.4% (n=78)
- Warfarin was predominantly reported (81.5%, n=677), followed by rivaroxaban (11.9%, n=99), dabigatran (3.6%, n=30), and apixaban (2.2%, n=18)
- 78.7% (n=654) of errors involved adults aged 60 years or older
  - More than one-third (34.4%, n=286) involved adults aged 80 years or older
- Nearly one-third of cases (29.4%, n=244) were reported as having an NCC MERP harm score of D to F

Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61. National Coordinating Council for Medication Error Reporting and Prevention [website]. [www.nccmerp.org/types-medication-errors](http://www.nccmerp.org/types-medication-errors). Accessed February 6, 2018.

## Dose Omissions

- Risk of a thromboembolic event
- Reasons varied
  - Medication not being ordered (eg, warfarin)
  - Orders not being administered (eg, orders "held" or transitions of care)
  - Orders being processed incorrectly (eg, system defaults)

Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

## Extra-Dose Errors

- Increased risk of bleeding events
- Reasons
  - Not "holding" warfarin after elevated INR
  - Change in clinicians
  - Communication errors
  - Patient's MAR not thoroughly reviewed

MAR = medication administration record.  
Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

## Error Type “Other”

- Prescribing errors (29.2%, n=45)
  - Primarily involved duplication of therapy
  - “Bridging”
- Incomplete medication list (13.0%, n=20)
  - Particularly during transitions of care

Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

## Duplication of Therapy

*“The patient was receiving heparin 5000 units [subcutaneously] every 8 hours for DVT prophylaxis.*

*Later in the day, apixaban 5 mg BID was also prescribed. The heparin was **not** discontinued.*

*Therefore, the patient received subcutaneous heparin while receiving therapeutic anticoagulation with apixaban.”*

DVT = deep vein thrombosis.  
Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

## Anticoagulation Bridging

*“Physician wrote orders for dabigatran, subcutaneous Lovenox,<sup>®</sup> and warfarin. The medications were not administered, and all orders were discontinued by the physician except for the Lovenox.”*

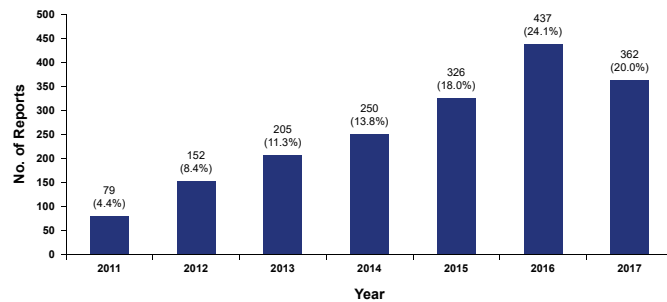
Andreica I, et al. *Pa Patient Saf Advis.* 2015;12(2):54-61.

The screenshot shows the Patient Safety Authority (PSA) website. The main content area displays a document titled "Identifying Patient Harm from Direct Oral Anticoagulants" dated June 15, 2018. The document is categorized under "Patient Safety Topics" and "Advisories & Events". It includes a "Share" button, a "Print" button, and a "Primary Audience" dropdown menu. The document is authored by Valentine D, et al. and is available in PDF format. The abstract section is visible, discussing the risks of direct oral anticoagulants (DOACs) compared to warfarin. The introduction section is also visible, mentioning the prevalence of atrial fibrillation in the United States and the use of DOACs.

Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2).  
[http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

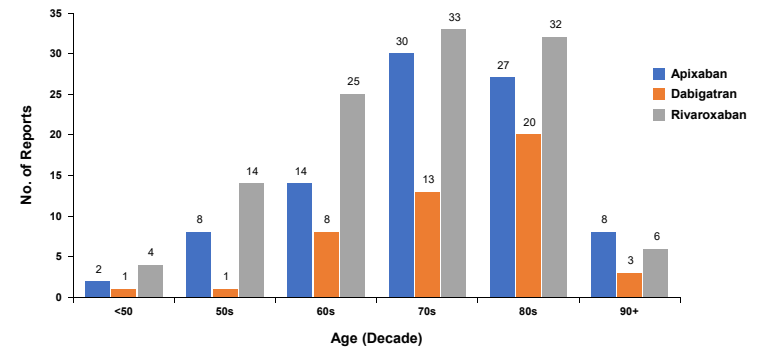
## Review of Adverse Drug Events Involving Direct Oral Anticoagulants

Number of Events Involving Direct Oral Anticoagulants by Event Year (N=1811)



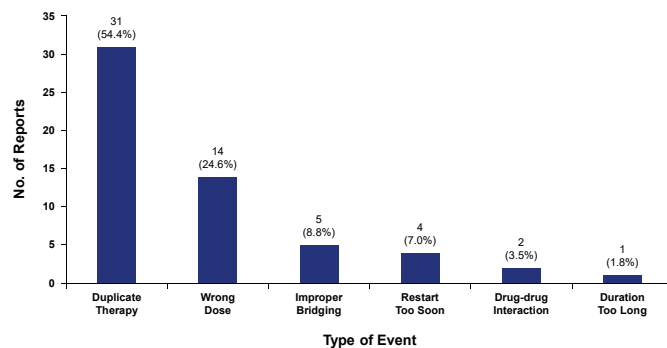
Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

## Adverse Events Involving Direct Oral Anticoagulants by Decade of Patient Age (N=249)



Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

## Types of Preventable Adverse Events Involving Direct Oral Anticoagulants (N=57)



Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

## Example of Duplicate Therapy

- 78-year-old patient had hip surgery in the fall and has not been as mobile since. She has recently started ambulating
- She presented to the ED [emergency department] with left lower extremity swelling and pain and was diagnosed with a DVT
- The ED physician wrote for Lovenox [enoxaparin] 130 mg subcutaneously and decided to admit the patient to the hospital
- The inpatient physician came to see the patient and prescribed Xarelto [rivaroxaban] 15 mg 2 hours after the Lovenox [enoxaparin] was administered
- The patient had a significant gastrointestinal bleed 24 hours after the duplicate therapy was administered. The patient went into shock and was transferred to the ICU [intensive care unit]. The patient was given factor IX, fresh frozen plasma, and packed red blood cells

Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

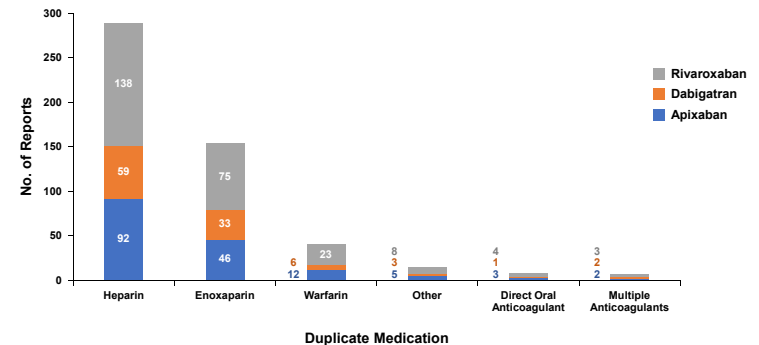


## Examples of Bridging Errors

- 87-year-old male patient received warfarin. Dabigatran was started as a "bridge to Coumadin therapy." Patient transferred to ICU. Patient developed bilateral nasal bleeding. Received vitamin K, fresh frozen plasma, and packed RBCs. The aPTT [activated partial thromboplastin time] result was elevated
- 92-year-old female patient admitted with hydropneumothorax. Had been taking apixaban 2.5 mg bid [twice a day] at home, and this was resumed [on the fourth day of the admission]. [Four days later] she was also started on warfarin 5 mg with plan to continue apixaban x 3 doses as bridge. [The next day the patient] was noted to have hematuria, INR = 1.6. Apixaban was discontinued and warfarin was continued. INR [the next day] was 1.7 with no additional bleeding documented

Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

## Medications Involved in Therapeutic Duplication Errors without Harm (N=515)



Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

## Effects on Procedure Cancellations

- Outpatient procedure cancellations and complications due to patients either holding or not holding their direct oral anticoagulants were noted in 7.6% (n=137 of 1811) of reports
- In 88.3% (n=121 of 137) of those reports, the procedure was canceled when the direct oral anticoagulant had not been held

Valentine D, et al. Identifying Patient Harm from Direct Oral Anticoagulants. *Pa Patient Saf Advis.* 2018 Jun;15(2). [http://patientsafety.pa.gov/ADVISORIES/Pages/201806\\_DOACs.aspx](http://patientsafety.pa.gov/ADVISORIES/Pages/201806_DOACs.aspx). Accessed July 16, 2018.

## Risk-Reduction Strategies

- Focus on system-based causes
  - Constraints
  - Standardization
  - Redundancies
  - Education and information
  - Monitoring of adverse drug events

## Constraints

- A pharmacist's review prior to dispensing
  - No overrides!
- Functional drug alerts (eg, hard stops)
- Elimination of verbal orders
- "Read-back" method in case of emergency verbal order

Andreica I, et al. *Pa Patient Saf Advis*. 2015;12(2):54-61.

## Standardization

- Prescribing
  - Required baseline information
  - Updating computer systems and healthcare records
  - "Hold" orders
  - Anticoagulation management service (AMS) programs for dosing, monitoring, and teaching patients
  - Rapid or emergency reversal of anticoagulation
  - Incomplete or "blank" orders
  - "NOAC"

Institute for Safe Medication Practices [website]. [www.ismp.org/Newsletters/acutecare/articles/20070111.asp](http://www.ismp.org/Newsletters/acutecare/articles/20070111.asp). Accessed February 6, 2018.

## Standardization

- Dispensing and administration
  - Administer warfarin at standard time
  - Eliminate limited selection of medications in the formulary, if possible
  - Define policies and procedures for therapeutic substitution or ways to approve use of a patient's own medication

Pharmacy Times [website]. <http://www.pharmacytimes.com/publications/health-system-edition/2013/july2013/new-oral-anticoagulants-implications-for-health-systems>. Accessed February 6, 2018.

## Redundancies

- Strategically placed, independent double checks
- Clinical decision support in computerized order entry
- Bar-code scanning

Institute for Safe Medication Practices [website]. [www.ismp.org/Newsletters/acutecare/articles/20070111.asp](http://www.ismp.org/Newsletters/acutecare/articles/20070111.asp). Accessed February 6, 2018.

## Therapeutic Monitoring

- Baseline laboratory test results need to be available in a timely manner
- Process control charts
  - To display trends of daily INR values

Institute for Safe Medication Practices [website]. [www.ismp.org/Newsletters/acute/articles/200701111.asp](http://www.ismp.org/Newsletters/acute/articles/200701111.asp). Accessed February 6, 2018.

## Education and Information

### • Staff

- Annual competence assessments
- New anticoagulant in the organization's formulary
- Underlying protocol (such as reversal protocols)
- Expertise in therapy management

### • Patient

- Remind patients that the risks of anticoagulants include bleeding
- Patient's ability to afford and purchase the medicine
- Provide education a couple days prior to discharge

Institute for Safe Medication Practices [website]. [www.ismp.org/Newsletters/acute/articles/200701111.asp](http://www.ismp.org/Newsletters/acute/articles/200701111.asp). Accessed February 6, 2018.

## Monitoring of Adverse Drug Events

- Adverse drug event triggers
  - INR >6
  - Bleeding
  - Administration of reversal agents

Adverse Drug Event Trigger Tool. Centers for Medicare & Medicaid Services (CMS). <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/QAPI/Downloads/Adverse-Drug-Event-Trigger-Tool.pdf>.

## Free Tools to Address Anticoagulants



Institute for Safe Medication Practices [website]. [www.ismp.org](http://www.ismp.org). Accessed February 6, 2018.

## Conclusions

- Oral anticoagulants are considered high-alert medications
- Complexity of the target-specific agents introduces more opportunities for errors
- Effective risk-reduction strategies will help hospitals minimize the occurrence of preventable oral-anticoagulant-related adverse events

Questions?

# Recognizing and Managing VOD in Affected and At-Risk Patient Populations



10  
YEARS

## Faculty

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## Disclosures

**Dr. Fausel** has disclosed no relevant financial relationships with any commercial interest.

## Learning Objectives

- Outline the risk factors and diagnostic criteria associated with VOD for the timely identification of at-risk and affected patients
- Distinguish among traditional and newer approaches to VOD management with respect to their clinical rationale for use, efficacy, safety, and tolerability
- Evaluate the available evidence surrounding the clinical and cost benefits of early or preventative VOD treatment in key patient populations
- Integrate the latest clinical evidence and expert recommendations into strategies to overcome barriers to optimal VOD diagnostic and therapeutic practices

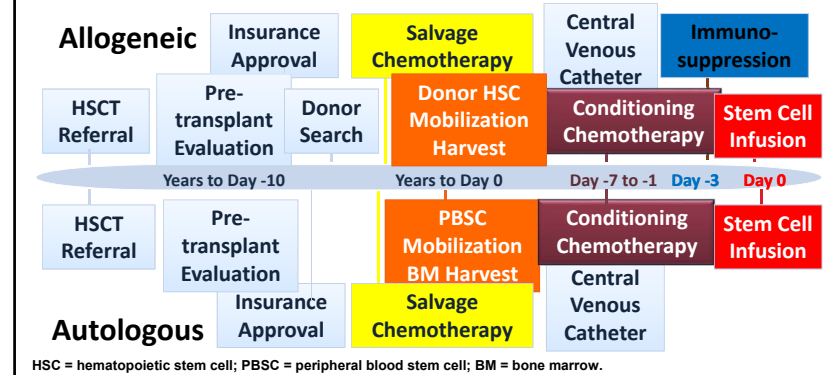
VOD = veno-occlusive disease.

## Veno-Occlusive Disease

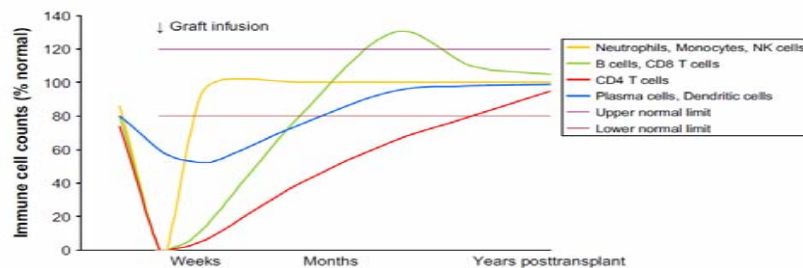
- Veno-occlusive disease (VOD) is also commonly known as sinusoidal obstructive syndrome (SOS)
- Life-threatening complication that occurs after HSCT
- Incidence is 8% to 14%, depending on the diagnostic criteria used
- Recent literature review of 135 published reports found the mean incidence to be 13.7%
- Incidence and prevalence depend on the portion of patients at high risk and exposure to predisposing agents

SOS = sinusoidal obstructive syndrome; HSCT = hematopoietic stem cell transplantation.  
Dalle JH, et al. *Biol Blood Marrow Transplant.* 2016;22(3):400-409. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168.

## HSCT Process

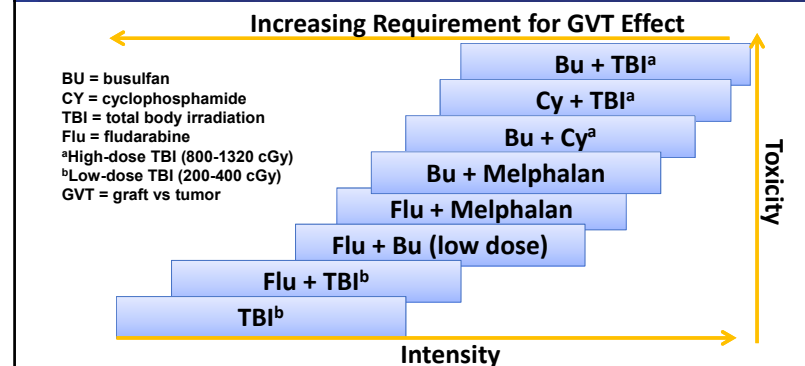


## Immune Reconstitution after HSCT



NK = natural killer; CD = cluster of differentiation.  
Tomblin M, et al. *Biol Blood Marrow Transplant.* 2009;15:1143-238.

## HSCT Conditioning Dose Intensity



## Commonly Used Preparative Regimens

Preparative Regimen	Days of Treatment	Designation
Fludarabine 25 mg/m <sup>2</sup> /d IV TBI 200 cGy	Days -4, -3, -2 Day 0	Non-myeloablative
Fludarabine 30 mg/m <sup>2</sup> /d IV Busulfan 10 mg/kg/d IV daily	Days -10 through -6 Days -4 through -1	Reduced-intensity conditioning
Fludarabine 25 mg/m <sup>2</sup> /d IV Melphalan 100-180 mg/m <sup>2</sup> IV	Days -6 to -2 Day -2	Reduced-intensity conditioning
Carmustine 300 mg/m <sup>2</sup> IV Etoposide 200 mg/m <sup>2</sup> IV Q12H Cytarabine 200 mg/m <sup>2</sup> IV Melphalan 140 mg/m <sup>2</sup> IV	Day -6 Days -5 through -2 Days -5 through -2 Day -1	Myeloablative
Cyclophosphamide 60 mg/kg/d TBI 200-200 cGy twice daily	Days -5, -4 Days -3, -2, -1	Myeloablative

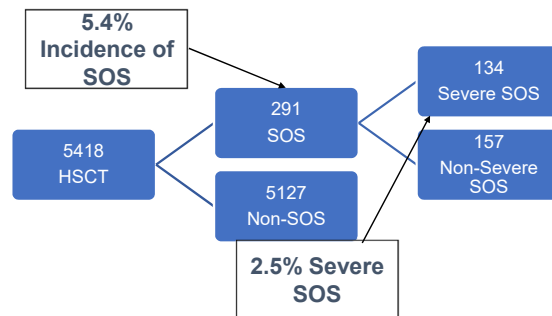
Bensinger WL. In: *Thomas' Hematopoietic Cell Transplantation*. 4th ed. John Wiley and Sons. 2009:316-332. Sandmaier BM and Storb R. In: *Thomas' Hematopoietic Cell Transplantation*. 4th ed. John Wiley and Sons. 2009:1043-1058.

## Common Complications of HCST

Autologous	Allogeneic
Nausea/vomiting Myelosuppression/aplasia Mucositis Bleeding Infection (eg, bacterial, fungal, viral) Conditioning-regimen specific end-organ dysfunction • VOD/SOS • IPS • Renal toxicity Late complications (eg, endocrinopathies, cataracts, continued myelosuppression, secondary malignancies)	Nausea/vomiting Myelosuppression/aplasia Mucositis Bleeding Infection (eg, bacterial, fungal, viral) Conditioning-regimen specific end-organ dysfunction • VOD/SOS • IPS • Renal toxicity Late complications (eg, endocrinopathies, cataracts, continued myelosuppression, secondary malignancies) Thrombotic microangiopathy GvHD – acute and chronic

GvHD = graft vs host disease.  
Gyurkocza B, et al. *Blood*. 2014;124:344-353.

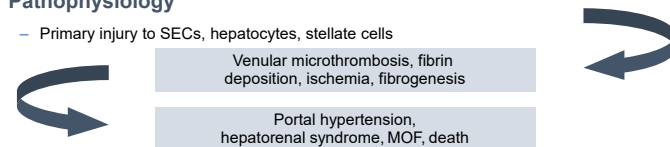
## Burden of VOD



Cao Z, et al. *J Med Econ*. 2017;20(8):871-883.

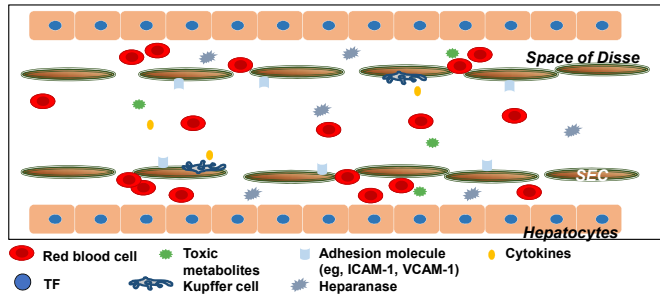
## Hepatic VOD Post-HSCT

- **Definition**
  - Also known as SOS
  - Hepatomegaly (painful), jaundice (bilirubin  $\geq 2$  mg/dL)
  - Fluid retention, weight gain ( $\geq 5\%$ ), ascites
  - Onset first 3-4 weeks post-HSCT, other causes absent
- **Pathophysiology**
  - Primary injury to SECs, hepatocytes, stellate cells



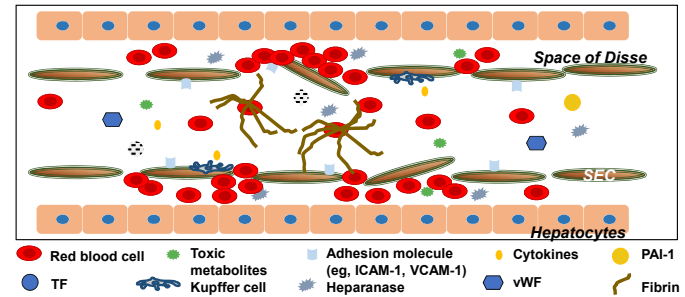
SEC = sinusoidal endothelial cell; MOF = multi-organ failure.  
Ho VT, et al. *Semin Thromb Hemost*. 2007;33(4):373-388; EBMT-ESH handbook [website]. <https://ebmt.online.forumservice.net>. Accessed September 6, 2017. Bearman SI. *Blood*. 1995;85(11):3005-3020.

## Activation and Damage to the Sinusoidal Endothelium (SEC)



↑TNF- $\alpha$ , ICAM-1, VCAM-1, PAI-1, vWF, TF, heparanase, ↓t-PA  
 ICAM-1 = intercellular adhesion molecule 1; VCAM-1 = vascular adhesion molecule 1; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; TF = tissue factor, t-PA = tissue-plasminogen activator.  
 Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136.

## Gap Formation, Fibrin Deposition, and Narrowing of the Sinusoids



↑TNF- $\alpha$ , ICAM-1, VCAM-1, PAI-1, vWF, TF, heparanase, ↓t-PA

Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136.

## Risk Factors for VOD

Biologic/Environmental	Iatrogenic
Pre-existing liver disease	Inotuzumab ozogamicin, gemtuzumab ozogamicin
Heparanase gene single nucleotide polymorphisms	HSCT conditioning with: <ul style="list-style-type: none"> <li>- Busulfan/cyclophosphamide</li> <li>- Melphalan</li> </ul>
Pyrrolizidine alkaloids	Abdominal irradiation
	Second myeloablative transplantation or transplantation beyond 2nd remission

Valla DC, et al. *Clin Res Hepatol Gastroenterol.* 2016;40:378-385.

## Clinical Criteria for the Diagnosis of VOD

Seattle Criteria	Baltimore Criteria
Presence before day 30 post-SCT of two or more of the following <ul style="list-style-type: none"> <li>• Jaundice</li> <li>• Hepatomegaly, right upper quadrant pain</li> <li>• Ascites +/- unexplained weight gain</li> </ul>	Hyperbilirubinemia >2 mg/dL before day 21 post-SCT and at least two of the following <ul style="list-style-type: none"> <li>• Hepatomegaly</li> <li>• Ascites</li> <li>• Weight gain <math>\geq 5\%</math> from baseline</li> </ul>
Modified Seattle Criteria	
Presence before day 20 post-SCT of two of the following <ul style="list-style-type: none"> <li>• Bilirubin &gt;2 mg/dL (<math>\sim 34 \mu\text{mol/L}</math>)</li> <li>• Hepatomegaly, right upper quadrant pain of liver origin</li> <li>• Unexplained weight gain of &gt;2% baseline because of fluid accumulation</li> </ul>	

- Both have high specificity of 91% to 92%, but low sensitivity

McDonald GB, et al. *Hepatology.* 1984;4(1):116-122. McDonald GB, et al. *Ann Intern Med.* 1993;118(4):255-267. Jones RJ, et al. *Transplantation.* 1987;44(6):778-783. Carreras E, et al. *Ann Hematol.* 1993;66(2):77-80.



## New EBMT Criteria for VOD/SOS Diagnosis in Children and Adults

### Children

- No limitation for time of onset of VOD/SOS
- Presence of  $\geq 2$  of the following<sup>a</sup>:
  - Unexplained consumptive and transfusion-refractory thrombocytopenia<sup>b</sup>
  - Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics
- OR
- a weight gain  $>5\%$  above baseline value
- Hepatomegaly (best if confirmed by imaging)<sup>c</sup> above baseline value
- Ascites (best if confirmed by imaging)<sup>c</sup> above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days
- OR
- bilirubin  $\geq 2$  mg/dL within 72 hours

### Adults

- Classical VOD/SOS ( $\leq 21$  days post-HSCT)
- Bilirubin  $\geq 2$  mg/dL and 2 of the following:
  - Painful hepatomegaly
  - Weight gain  $>5\%$
  - Ascites
- Late-onset VOD/SOS ( $>21$  days post HSCT)
- Classical VOD/SOS beyond day 21
- OR
- Histologically proven VOD/SOS
- OR
- Presence of  $\geq 2$  of the following:
  - Bilirubin  $\geq 2$  mg/dL (or  $34 \mu\text{mol/L}$ )
  - Painful hepatomegaly
  - Weight gain  $>5\%$
  - Ascites
- And hemodynamic and/or ultrasound evidence of VOD/SOS

<sup>a</sup>With the exclusion of other potential differential diagnoses; <sup>b</sup> $\geq 1$  weight-adjusted platelet transfusion/day to maintain institutional guidelines; <sup>c</sup>Suggested: imaging (ultrasound, computed tomography, or magnetic resonance imaging) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.  
Corbacioglu S, et al. *Expert Rev Gastroenterol Hepatol.* 2017;11(10):885-898.

## Prognosis of VOD/SOS

### • Most useful

- Rate of rise of bilirubin
- Rate of weight gain
- MOF
  - Oxygen requirement
  - Renal dysfunction
  - Encephalopathy

} Bearman model

### • sVOD

- MOF has emerged as the best parameter (to date) for predicting bad outcome
- All-cause mortality  $>80\%$
- Previous standard: best supportive care

sVOD = severe veno-occlusive disease.

Bearman SI, et al. *J Clin Oncol.* 1993;11(9):1729-1736. Cesaro S, et al. *Haematologica.* 2005;90(10):1396-1404. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168. McDonald GB, et al. *Ann Intern Med.* 1993;118(4):255-267. Bulley SR, et al. *Pediatr Blood Cancer.* 2007;48(7):700-704. Lee SH, et al. *Bone Marrow Transplant.* 2010;45(8):1287-1293. Wadleigh M, et al. *Curr Opin Hematol.* 2003;10(6):451-462. Pinusch M, et al. *Transplantation.* 2005;80(10):1376-1382. Cheuk DK, et al. *Bone Marrow Transplant.* 2007;40(10):935-944.

## Management of VOD

- Management strategies primarily consist of supportive measures
  - Diuresis, paracentesis, hemofiltration, mechanical ventilation, and hemodialysis
  - Not all of these strategies lead to improved outcome
- Heparin plus t-PA
  - Response in up to 30% of patients, but survival is poor
  - Associated with increased risk of life-threatening bleeding
  - Not recommended in patients with sVOD who have already developed MOF
  - Should also be avoided in patients with pulmonary or renal failure

DeLeve LD, et al. *Hepatology.* 2009;49(5):1729-1764. Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Bearman SI, et al. *Blood.* 1997;89(5):1501-1506.

## t-PA with or without Heparin for the Treatment of VOD

Author	No. of Patients	Dose (mg/d)	Duration (d)	Heparin (yes/no)	No. of Responses	Life-Threatening Hemorrhage
Baglin, et al (1990)	1	50	4	No	1	0
Bearman, et al (1997)	42	5.4-120	2-4	Yes	12	10
Leahey, et al (1996)	9	5-10	2-4	Yes	5	0
Goldberg, et al (1996)	1	20	4	Yes	1	0
Higashigawa, et al (1995)	1	2-5	4	Yes <sup>a</sup>	1	0
Lee, et al (1996)	3	10-20	7-14	Yes	3	0
Yu, et al (1994)	3	0.25-0.5 <sup>b</sup>	4	No	2	0
Schriber, et al (1999)	37	30-40	1-25	Yes	13 <sup>c</sup> (2) <sup>d</sup>	13
Kulkarni, et al (1999)	17	10	1-12	Yes <sup>a</sup>	6	0

<sup>a</sup>Patient also received PGE; <sup>b</sup>Dose reported as mg/kg; <sup>c</sup>In patients who were suspected of VOD; <sup>d</sup>In patients who were diagnosed with VOD; \*12 patients received heparin.

## Current Management of VOD

- Liver transplantation can be beneficial
  - Only considered in patients with severe liver failure; feasibility a challenge
  - Generally contraindicated in cases of malignancy due to high rates of recurrence
- TIPS
  - Shown to relieve ascites in some patients (but in others, it worsened the process)

TIPS = transjugular intrahepatic portosystemic shunt.  
 Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Richardson PG, et al. *Acta Haematol.* 2001;106(1-2):57-68. DeLeve LD, et al. *Hepatology.* 2009;49(5):1729-1764. Azoulay D, et al. *Bone Marrow Transplant.* 2000;25(9):987-992.

## Rationale for Development of New Therapies for VOD/SOS

- Treatments are supportive and are associated with significant risk of bleeding
- sVOD remains a serious complication of SCT with a high mortality rate (>80%)

**There is an urgent, unmet clinical need for effective therapies for the treatment and prevention of VOD/SOS**

Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Bearman SI, et al. *Blood.* 1997;89(5):1501-1506. Coppel JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168.

## Novel Therapeutic Approaches: Goals

- Modulate endothelial cell (EC) injury without causing systemic bleeding or other toxicity
- Protect host without compromising anti-tumor effect of cytotoxic therapy
- Preferably have activity in spectrum of vascular injury syndromes during SCT (eg, TTP/HUS, DAH/IP)
- Possible role in other syndromes underpinned by endothelial damage (eg, GvHD)

TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic-uremic syndrome; DAH = diffuse alveolar hemorrhage; IP = interstitial pneumonitis.  
 Richardson P, et al. *Br J Haematol.* 1999;107(3):485-493.

## Proposed Mechanism of Action of DF

- DF: A polydisperse oligonucleotide shown to exert protective effects on the endothelium
- Precise mechanism of action of DF is yet to be determined
- Proposed to involve two distinct elements
  - Protection of ECs
  - Restoration of the thrombotic–fibrinolytic balance
- DF
  - Decreases the influx of inflammatory mediators (↓ICAM-1 and heparanase)
  - Activates the fibrinolytic system (↑t-PA, TFPI and thrombomodulin, ↓PAI-1, TF and vWF)

TFPI = tissue factor pathway inhibitor.  
 Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136. Guglielmelli T, et al. *Expert Opin Biol Ther.* 2012;12(3):353-361. Pellegatta F, et al. *Br J Pharmacol.* 1996;118(3):471-476. Echert C, et al. *Bone Marrow Transplant.* 2010;45(suppl 2):S281. Ostrovsky O, et al. *Blood.* 2010;115(11):2319-2328. Falanga A, et al. *Leukemia.* 2003;17(8):1636-1642. Morabito F, et al. *Expert Opin Biol Ther.* 2009;9(6):763-772. Palomo M, et al. *Biol Blood Marrow Transplant.* 2011;17(4):497-506. Zhou Q, et al. *Thromb Hemost.* 1994;71(4):507-510. Cella G, et al. *Clin Appl Thromb Hemost.* 2001;7(3):225-228.

## Pivotal Treatment Trial: Historically Controlled, Multi-Center, Open-Label, Phase 3 Study; 2005-01

### • Primary objective

- To demonstrate the efficacy of DF 25 mg/kg/d in patients with severe VOD in terms of CR rate by day +100 post-HSCT
  - CR defined as total bilirubin <2 mg/dL and resolution of MOF

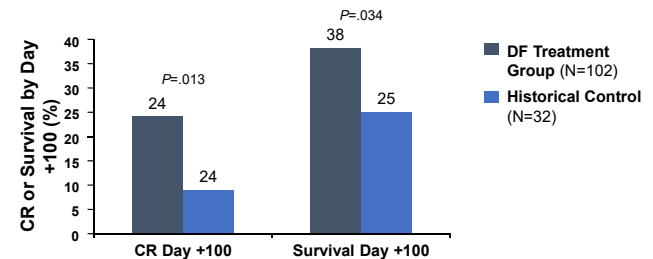
### • Secondary objectives

- To compare survival rates at day +100 and day +180 post-HSCT in patients receiving DF with those in the HC cohort
- To assess the safety of the selected dose and schedule of DF in patients with severe VOD
- 134 eligible patients** (based on Baltimore criteria by day +21 and either renal and/or pulmonary failure by day +28)
  - DF arm (n=102), DF 25 mg/kg/d<sup>a</sup>, median treatment duration: 22 days (range, 1-60 days), minimum 21 days
  - HC arm (n=32), subjects selected by an independent Medical Review Committee blinded to outcome

<sup>a</sup>DF given IV in four divided doses ~every 6 hours.

Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

## Phase 3 Results: DF Significantly Increased CR and Survival at Day +100



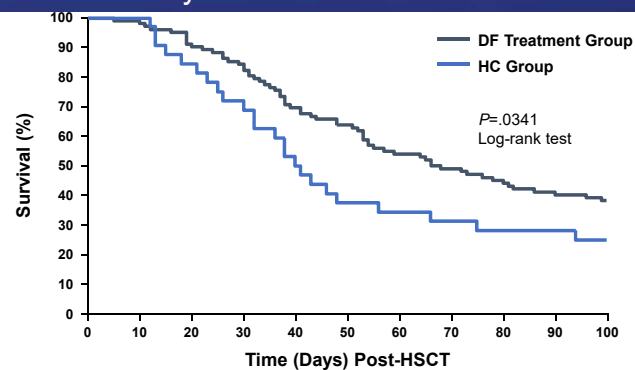
### • AEs

- Hemorrhagic AEs were similar between treatment and control arms (65% vs 69%)
- 18% of treated patients experienced a drug-related toxicity that led to discontinuation

AE = adverse event.

Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

## Phase 3 Results: DF Demonstrates a Significant Survival Benefit at Day +100 in Patients with Severe VOD



Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG. Oral presentation at EBMT 2013, London, UK.

## Phase 3: Summary

- DF improves CR and survival at day +100 post-HSCT
- DF was generally well tolerated
- Toxicities observed in this study were similar to those observed in previous studies

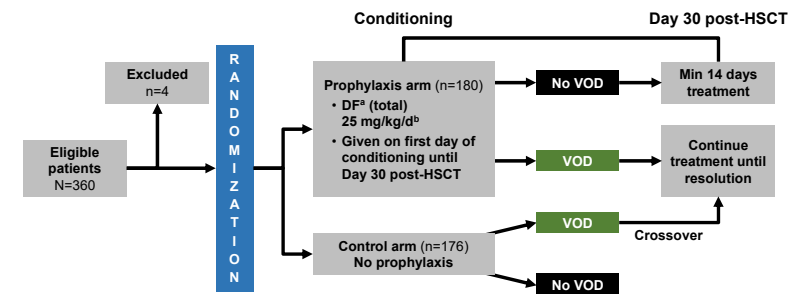
Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

## EBMT Phase 3 Study with DF for the Prevention of VOD in HSCT Patients

- Open-label, randomized controlled trial in pediatric patients (aged <18 years)
- Objective: To assess whether prophylactic use of DF can reduce the incidence and severity of VOD in high-risk pediatric patients undergoing HSCT
- Primary endpoint: Development of VOD by day 30 post-HSCT
- Secondary endpoints: Assessment of VOD severity and incidence and severity of acute GvHD (aGvHD)
- 356 eligible patients randomized to
  - Prophylaxis arm (n=180), DF<sup>a</sup> (total) 25 mg/kg/d<sup>a</sup> given on first day of conditioning until day 30 post-HSCT
  - Control arm (n=176), no prophylaxis

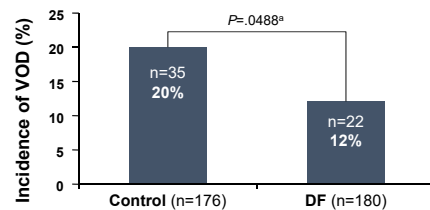
<sup>a</sup>DF given IV in four divided doses of 6.25 mg/kg over 2 hours.  
Corbacioglu S, et al. *Lancet*. 2012;379(9823):1301-1309.

## EBMT Phase 3 Prevention: Study Design



<sup>a</sup>Designated an orphan drug by the FDA and EMA; <sup>b</sup>DF given IV in four divided doses of 6.25 mg/kg over 2 hours.  
Corbacioglu S, et al. *Lancet*. 2012;379(9823):1301-1309.

## Phase 3 Prevention Results: DF Significantly Reduced the Incidence of VOD in Children



- No significant difference between VOD-associated mortality at 100 days after HSCT in DF vs control group (2% vs 6%,  $P=.10$ )
- However, mortality was four times higher in patients with VOD than those without VOD (25% vs 6%,  $P<.0001$ )

<sup>a</sup>Z test for competing risk analysis.  
Corbacioglu S, et al. *Lancet*. 2012;379(9823):1301-1309.

## Updated Results from a Large Treatment IND Study Using DF for Patients with Hepatic VOD

Paul G. Richardson, MD; Angela R. Smith, MD, MS; Brandon M. Triplett, MD; Nancy A. Kernan, MD; Stephan A. Grupp, MD, PhD; Sally Arai, MD; Joseph H. Antin, MD; Leslie Lehmann, MD; Valeria Bandiera; Maja Miloslavsky, PhD; Robin Hume, MS; Alison L. Hannah, MD; Bijan Nejadnik, MD; Robert J. Soiffer, MD; and the Defibrotide Study Group

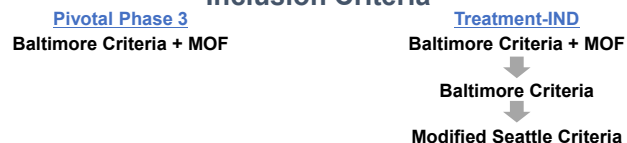
2015 BMT Tandem Meetings, February 11-15, San Diego, California

- Inclusion by one of the following
  - Clinical VOD diagnosis
    - Originally, severe VOD (with MOF) per Baltimore criteria post HSCT was required
    - Study was amended to include non-severe VOD and VOD per modified Seattle criteria following HSCT or chemotherapy
  - Biopsy-proven VOD
- Exclusion: Clinically significant bleeding or the need for  $\geq 2$  vasopressors, concurrent use of medication that increases risk of hemorrhage

Jones RJ, et al. *Transplantation*. 1987;44(6):778-783. McDonald G, et al. *Ann Intern Med*. 1993;118(4):255-267. Carreras E, et al. *Ann Hematol*. 1993;66(2):77-80.

## Pivotal Phase 3 Trial vs Treatment-IND

### Inclusion Criteria



	Pivotal Phase 3		T-IND
	DF	Control	DF
sVOD/MOF	102	32	279
VOD (no MOF)	0	0	247
Total post-HSCT	102	32	526

Jones RJ, et al. *Transplantation*. 1987;44(6):778-783. McDonald G, et al. *Ann Intern Med*. 1993;118(4):255-267. Carreras E, et al. *Ann Hematol*. 1993;66(2):77-80. Richardson PG, et al. *Blood*. 2009;114(22):654. Richardson PG, et al. *Blood*. 2016;127(13):1656-1665.

## Summary of AEs

- Tolerability and low rate of DF-associated toxicities consistent with prior studies

Category	Overall, n (%) (N=641)
≥1 AE	429 (67)
≥1 Grade 3/4/5 AE	346 (54)
≥1 AE leading to discontinuation	176 (28)
≥1 Treatment-related AE <sup>a</sup>	135 (21)

<sup>a</sup>Considered to be possibly, probably, or definitely related to DF treatment. Missing relationships were analyzed as "possibly related."  
 Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

## Most Common Treatment-Related AEs

AE <sup>a</sup> (Incidence ≥5%)	Overall, n (%) (N=641)
Hypotension	86 (13)
Respiratory failure	49 (8)
Diarrhea	48 (8)
Pyrexia	47 (7)
Pulmonary hemorrhage	44 (7)
Renal failure	44 (7)
Vomiting	38 (6)
Gastrointestinal hemorrhage	35 (6)
Hypoxia	35 (6)
Epistaxis	33 (5)
Nausea	32 (5)

<sup>a</sup>Other than worsening MOF and VOD.  
 Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

## Survival at Day +100 Pediatric and Adult Subgroups

- Survival at day +100 in post-HSCT patients was 58% in the pediatric subgroup and 45% in the adult subgroup

Subgroup	Pediatric (≤16 years) Survival Day +100 n/N (%)	Adult (>16 years) Survival Day +100 n/N (%)
All HSCT patients	163/283 (58)	109/243 (45)
sVOD/MOF	79/157 (50)	46/122 (38)
VOD (no MOF)	84/126 (67)	63/121 (52)
All post-chemotherapy patients	39/47 (83)	9/15 (60)

Note: Chemotherapy patients with non-sVOD not analyzed separately.  
 Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

## Survival at Day +100 Allograft and Autograft Subgroups

- Survival at day +100 in post-HSCT patients was 50% in allograft patients and 66% in autograft patients

Subgroup	Allografts Survival Day +100 n/N (%)	Autografts Survival Day +100 n/N (%)
<b>All HSCT patients</b>	234/467 (50)	37/56 (66)
<b>sVOD/MOF</b>	109/252 (43)	16/27 (59)
<b>VOD (no MOF)</b>	125/215 (58)	21/29 (72)

Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

## Survival at Day +100

- Survival at day +100 in post-HSCT patients was 52%

Subgroup	Survival Day +100 n/N (%)
<b>All HSCT patients</b>	272/526 (52)
<b>sVOD/MOF</b>	125/279 (45)
<b>VOD (no MOF)</b>	147/247 (60)
<b>All post-chemotherapy patients</b>	48/62 (77)

Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

## Conclusions

- Largest prospective evaluation of DF to date in VOD
- DF was generally well tolerated in this population, with manageable toxicity, and highly consistent with prior studies of DF in this setting
  - Tolerability was consistent with the low incidence of DF-associated toxicities reported in prior studies
- Day +100 survival
  - Favorable results shown in pediatric, adult, allograft, and autograft subgroups post HSCT or chemotherapy with sVOD/MOF and VOD (no MOF)
  - Higher survival rate in VOD without MOF indicates further study is warranted to determine impact of treatment earlier in the course of VOD
- Future directions
  - Prophylaxis in allogeneic and high-risk autologous HSCT
  - Earlier treatment

Richardson PG, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017. Corbacioglu S, et al. *Lancet*. 2012;379(9823):1301-1309. Dignan FL, et al. *Br J Haematol*. 2013;163(4):444-457. Richardson PG, et al. *Blood*. 2013;122(21):2470.

## Defibrotide

- DF open-label studies in patients with hepatic VOD and MOD following HSCT
  - In one trial, treatment with DF was associated with a 38.2% survival rate compared with a 25% rate in matched historical controls
  - In another trial, the survival rate was 44%

MOD = multi-organ dysfunction.  
*Med Lett Drugs Ther*. 2016;58(1503):120.

## Socioeconomic Burden of VOD

- Existing burden of patients undergoing HSCT is already high
- Individuals with VOD are faced with
  - Increased hospital length of stay (average, 28 days)
  - Almost \$50,000 increase in health-related costs (~\$120,000 total)
  - Six times higher risk of mortality compared with patients without VOD

Dvorak CC, et al. *Biol Blood Marrow Transplant*. 2016;22(3):S275.

## Cost-Effectiveness: DF

- The recommended dosage of DF is 6.25 mg/kg given as a 2-hour IV infusion every 6 hours for a minimum of 21 days
- The cost of 21 days of treatment with DF for a patient weighing 70 kg is \$155,925
- Budget impact model from the perspective of a bone-marrow transplantation center
  - Estimated that 2.3% of adults and 4.2% of children would develop VOD with MOD following HSCT
- Incremental cost-effectiveness ratio (ICER) was \$47,736
  - 88% probability DF was cost-effective at a \$100,000/QALY threshold

QALY = quality-adjusted life year.

Veenstra DL, et al. *J Med Econ*. 2017;20(5):453-463.

## Cost-Effectiveness Prophylaxis: DF

- Evaluation of the cost-effectiveness of DF
  - Of 438 pediatric patients identified as having undergone HSCT, 138 were at risk of VOD (total incidence of VOD was 7.4%)
- Total calculated costs for prophylactic DF in 138 patients at risk was almost six times higher than the incremental costs for patients with VOD
- Concluded DF prophylaxis is not cost-effective
- Limitation: Cost analysis included all patients undergoing HSCT and not just those at risk of developing severe VOD

Pichler H, et al. *Biol Blood Marrow Transplant*. 2017;23(7):1128-1133.

## Medications for VOD

### Prevention<sup>a</sup>

- DF: Recommended based on risk
- Heparin: No longer recommended
- UDCA: Has shown reduction in VOD
- Pentoxifylline: Not recommended
- Antithrombin: Not recommended
- Prostaglandin E1: Not recommended

### Treatment

- DF: Recommended
- Tissue plasminogen activator: Not recommended
- N-acetylcysteine: Not recommended
- Methylprednisolone: May be considered
- Judicious clinical care: Recommended (fluid balance)
- Early discussions with specialists (critical care/hepatology)

<sup>a</sup>DF is currently not approved for preventative treatment but is in clinical trials for this indication.

UDCA = ursodeoxycholic acid.

Dignan FL, et al. *Br J Haematol*. 2013;163(4):444-457. ClinicalTrials.gov [website]. Study comparing efficacy and safety of defibrotide vs best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients. Last updated April 27, 2018. Accessed May 18, 2018.

## DF Prophylaxis

### Pediatrics

- Recommended at a dose of 6.25 mg/kg IV 4X/day with risk factors
  - Pre-existing hepatic disease
  - Second myeloablative transplantation
  - Allogeneic transplantation for leukemia beyond second relapse
  - Conditioning with busulfan-containing regimens
  - Prior treatment with gemtuzumab ozogamicin
  - Diagnosis of primary hemophagocytic lymphohistiocytosis
  - Adrenoleukodystrophy or osteopetrosis

1A

2B

### Adults

- Recommended at a dose of 6.25 mg/kg IV 4X/day with risk factors
  - Pre-existing hepatic disease
  - Second myeloablative transplantation
  - Allogeneic transplantation for leukemia beyond second relapse
  - Conditioning with busulfan-containing regimens
  - Prior treatment with gemtuzumab ozogamicin
  - Diagnosis of primary hemophagocytic lymphohistiocytosis
  - Adrenoleukodystrophy or osteopetrosis

Gokce M, et al. *Exp Clin Transpl*. 2013;11:440-446.

## Treatment Stratification

- Preventive measures
  - Resolve reversible risk factors (eg, acute hepatitis, iron overload)
  - Irreversible risk factors: Include patients on prophylaxis when possible (eg, second HCST, previous liver disease, radiation, or treatment with gemtuzumab ozogamicin)
- Monitor for VOD/SOS: Diagnose when appropriate and treat
- Severe VOD/SOS: Consider DF (start immediately in patients with multiple organ failure)

Carreras E. *Br J Haematol*. 2015;168(4):481-491.

## Summary

- VOD/SOS is a potentially life-threatening complication of HSCT
- In cases of sVOD/MOF, mortality rate can be as high as 80% or more
- Diagnosis of VOD/SOS relies on clinical criteria
- Current management of VOD/SOS primarily involves supportive care
- There is an urgent unmet need for better treatment strategies for the treatment and prevention of VOD/SOS
  - DF, a polydisperse oligonucleotide (which has orphan drug status for the treatment and prevention of VOD) is EMA-approved and commercially launched in the EU
  - The FDA approved DF on March 31, 2016, for the treatment of adult and pediatric patients with VOD with renal or pulmonary dysfunction following HSCT
- Phase 3 trial of DF prophylaxis in very high-risk pediatric and adult patients is ongoing

## Questions?



# Therapeutic Advances in Hyperkalemia

A Pharmacist's Guide to Patient Identification and Treatment



## Faculty

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## Disclosures

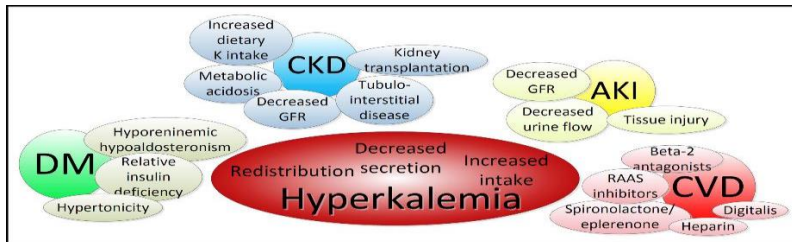
**Dr. Grabe** has disclosed no relevant financial relationships with any commercial interest.

Dr. Grabe will be discussing the following off-label: Patiromer and sodium zirconium cyclosilicate (formerly ZS-9) – hyperkalemia

## Learning Objectives

- Outline the clinical and socioeconomic consequences of unrecognized and undertreated chronic hyperkalemia
- Identify the risk factors and pathophysiologic mechanisms associated with the development of hyperkalemia in key patient populations
- Evaluate the latest clinical data surrounding new and emerging potassium binding agents with respect to mechanisms of action, efficacy, safety, indications, and therapeutic placement in hyperkalemia management strategies
- Advance the long-term management of hyperkalemia in pharmacy practice through measures that facilitate at-risk patient monitoring, promote patient/provider education, and integrate newer therapies for optimal patient outcomes

## Hyperkalemia



DM = diabetes mellitus; CKD = chronic kidney disease; GFR = glomerular filtration rate; AKI = acute kidney injury; CVD = cardiovascular disease.  
Kovesdy CP. *Am J Med.* 2015;128(12):1281-1287.

## Epidemiology and Cost of Hyperkalemia

- General population
  - 76,028 ED visits (2014)
  - 46% admitted
  - Average LOS, 3.3 days
  - Cost \$29,667 per stay
- CKD
  - Depends on severity
  - Depends on definition

Time Spent at Serum Potassium Levels			
eGFR (mL/min/1.73 m <sup>2</sup> )	Serum K <sup>+</sup> Level mEq/L		
	5.0-5.4	5.5-5.9	≥6.0
50-59	11.3	1.7	0.2
40-49	14.6	2.7	0.3
30-39	18.9	4.5	0.7
<30	23.0	7.6	1.8

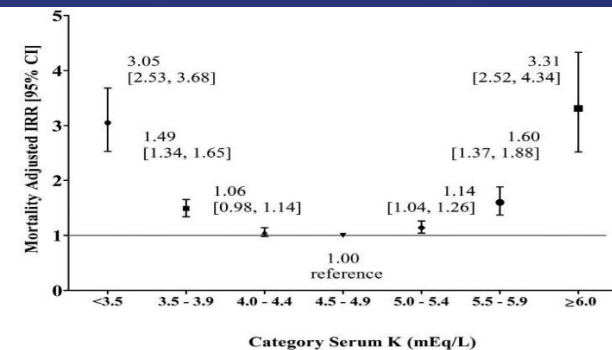
ED = emergency department; LOS = length of stay; eGFR = estimated glomerular filtration rate.  
AHRQ Agency for Healthcare Research and Quality [website]. <http://hcupnet.ahrq.gov/>. Accessed May 14, 2018. Luo J, et al. *Clin J Am Soc Nephrol.* 2016;11(1):90-100.

## Preventable Hospitalizations

- Measurement of inpatient encounters for **ambulatory care sensitive conditions**
  - Hyperkalemia, HF, malignant hypertension, volume overload
- Patients included if they had CKD (eGFR, 15-60 mL/min/1.73 m<sup>2</sup>)
- 1 in 4 CKD hospitalizations linked to ambulatory care sensitive conditions
- Majority of encounters were related to HF or hyperkalemia

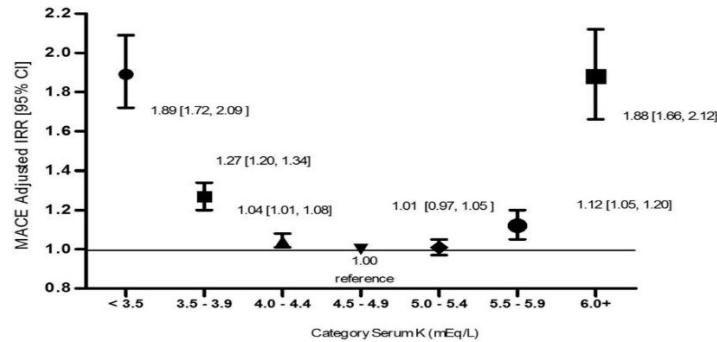
HF = heart failure.  
Ronksley PE, et al. *Clin J Am Soc Nephrol.* 2016;11(11):2022-2031.

## Associations between Serum K<sup>+</sup> and Mortality



Luo J, et al. *Clin J Am Soc Nephrol.* 2016;11:90-100.

## Major Adverse CV Events (MACE) According to Serum K<sup>+</sup>



Luo J, et al. *Clin J Am Soc Nephrol*. 2016;11:90-100.

## Drugs of Choice for Conditions

- Hypertension
  - ACEI
  - ARB
- HF
  - ACEI
  - ARB
  - Aldosterone antagonists
- Diabetic nephropathy
  - ACEI
  - ARB

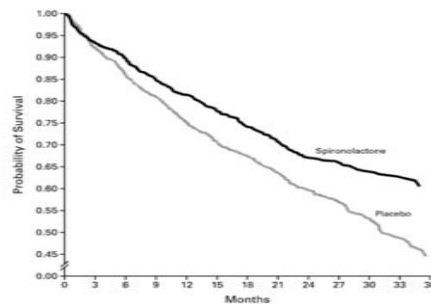
### Strategies for managing hypertension

- Maximize dose of one agent, then add a second agent
- Start one agent, then add a second agent before maximal dose
- Start two agents and titrate dose
- Follow the Dietary Approach to Stop Hypertension (DASH) diet

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DASH = dietary approach to stop hypertension.

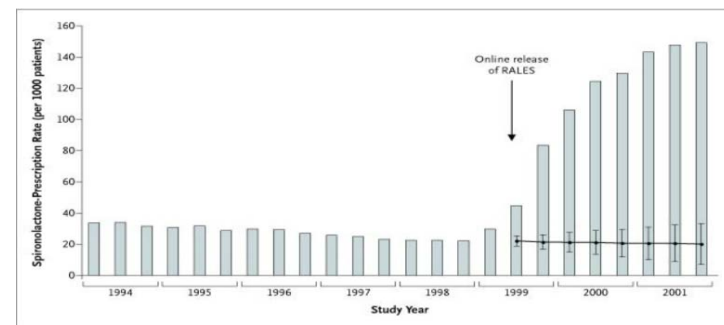
## RALES

- Severe HF
- Study terminated early
- 31% reduction in death



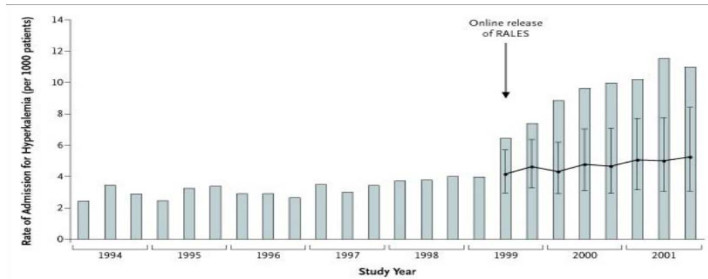
RALES = Randomized Aldactone Evaluation Study.  
Pitt B, et al. *N Engl J Med*. 1999;341(10):709-717.

## Use of Spironolactone Increased Dramatically



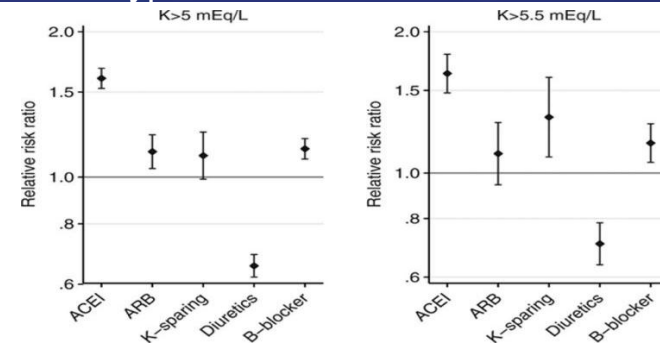
Juurlink DN, et al. *N Engl J Med*. 2004;351:543-551.

## So Did Hyperkalemia



Juurink DN, et al. *N Engl J Med.* 2004;351:543-551.

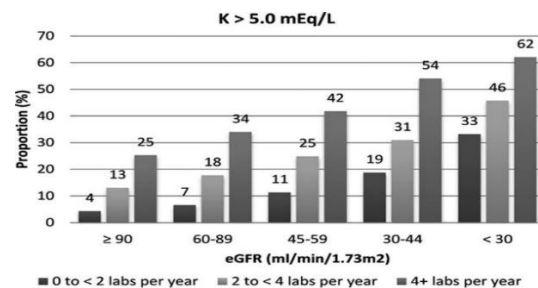
## Risk of Hyperkalemia Associated with Antihypertensive Medication Classes



K = potassium.

Chang AR, et al. *Hypertension.* 2016;67:1181-1188.

## Proportion Experiencing Hyperkalemia over 3 Years by eGFR and Frequency of Potassium Testing



Chang AR, et al. *Hypertension.* 2016;67:1181-1188.

## Case Study

- 53-year-old man with CKD stage 3b (eGFR, 34 mL/min/1.73 m<sup>2</sup>), type 2 diabetes mellitus, hypertension, dyslipidemia, and proteinuria
  - Current medications
    - Lisinopril 40 mg daily
    - Hydrochlorothiazide 25 mg daily
    - Atorvastatin 10 mg daily
    - Aspirin EC 81 mg daily
    - Metformin 1000 mg twice daily
    - Linagliptin 5 mg daily
  - Recent laboratory results show hyperkalemia with a serum potassium level of 5.5 mEq/L

Based on the clinical scenario, which of the following actions should be taken?

- A. Reduce dose of lisinopril
- B. Discontinue lisinopril
- C. Increase dose of hydrochlorothiazide
- D. Add furosemide 40 mg daily
- E. Add sodium polystyrene sulphonate



## Actions Taken after Hyperkalemia

Action	K >5.0 mEq/L	K >5.5 mEq/L	Control
ED visit	1.2%	3.1%	0.7%
Repeat serum K measurement	18.4%	44.3%	0.0%
Rx SPS	0.7%	4.7%	0.0%
Rx/Incr diuretic	5.6%	9.2%	2.5%
D/C ACEI or ARB	10.5%	24.3%	4.8%
Decr ACEI or ARB	2.6%	4.8%	1.2%
D/C K-sparing diuretic	23.0%	48.5%	7.5%
Decr K-sparing diuretic	1.4%	1.1%	0.5%

SPS = sodium polystyrene sulphonate; D/C = discontinuation.  
Chang AR, et al. *Hypertension*. 2016;67:1181-1188.

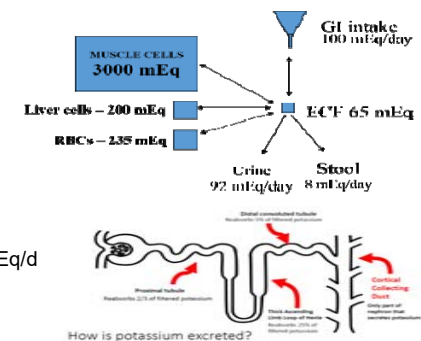
Which part of the nephron is responsible for potassium secretion?

- A. Proximal convoluted tubule
- B. Loop of Henle
- C. Distal convoluted tubule
- D. Cortical collecting duct

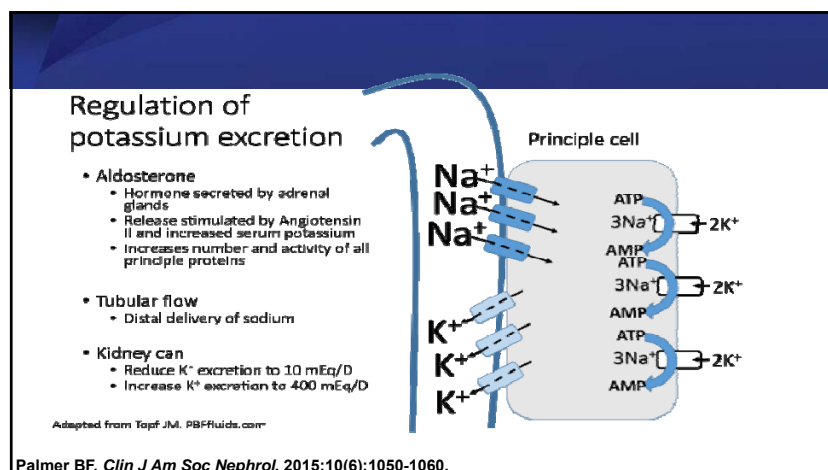
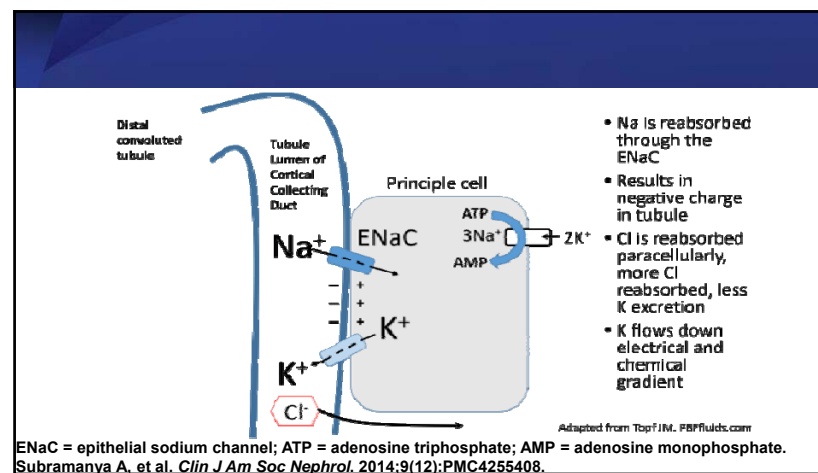
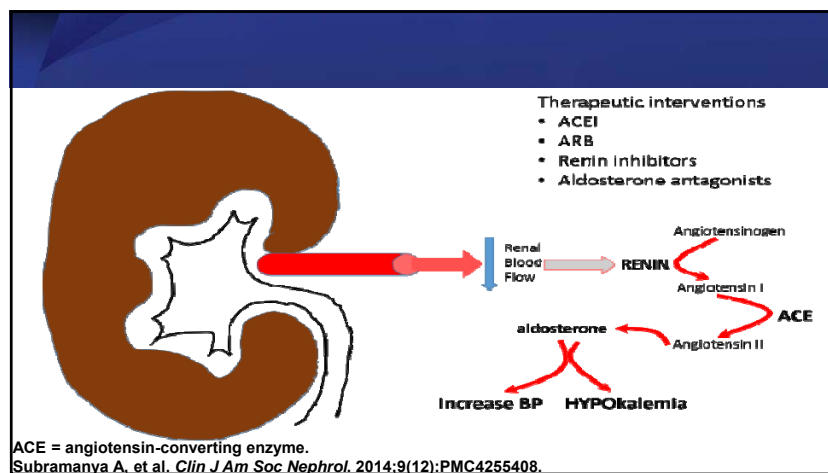


## Potassium Handling: What Is Normal?

- Intracellular cation (120-153 mEq/L)
  - Extracellular (3.5-4.5 mEq/L)
- Typical 70-kg man has 4000 mEq
  - 56 mEq = extracellular
  - Think about typical doses for potassium supplement
- Average US diet = 40 mEq/d
- Recommended daily allowance = 90 mEq/d



RBC = red blood cell; GI = gastrointestinal; ECF = extracellular fluid.  
Palmer BF, et al. *Adv Physiol Educ*. 2016;40:480-490.



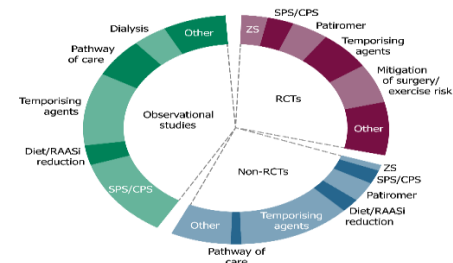
## Hyperkalemia Waits for No One

- Severe muscle weakness
- Electrocardiogram changes
- Conduction abnormalities
- Arrhythmia
- Reduced urinary acid secretion

UpToDate [website]. Mount DB. Clinical manifestations of hyperkalemia in adults. <https://www.uptodate.com/contents/clinical-manifestations-of-hyperkalemia-in-adults>. Last updated December 12, 2017. Accessed May 14, 2018.

## Management of Hyperkalemia

## Management of Hyperkalemia



ZS = sodium zirconium cyclosilicate; SPS/CPS = sodium/calcium polystyrene sulphonate; RCT = randomized controlled trial; RAASI = renin-angiotensin-aldosterone system inhibitor. Palaka E, et al. *Int J Clin Pract.* 2018;72(2):e13052.

Which of the following serious adverse events related to SPS resulted in an FDA safety labeling change?

- A. Exacerbation of HF
- B. Elevation of BP
- C. Development of colonic necrosis
- D. Risk of AKI



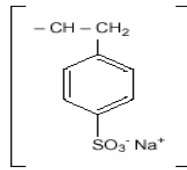
FDA = US Food and Drug Administration; BP = blood pressure.

## Current Therapies

- Current therapies for acute and chronic management of hyperkalemia
  - Temporizing agents
    - Insulin/Dextrose
    - Beta agonists (eg, albuterol)
    - Hemodialysis
  - Sodium polystyrene sulfonate (SPS)
  - Organic polymer resin patiromer calcium sorbitex (patiromer)
  - Sodium zirconium cyclosilicate (formerly ZS-9)

## Sodium Polystyrene Sulfonate (SPS)

- Benzene, diethenyl-polymer, with ethenylbenzene, sulfonated, sodium salt
- Contraindications: Hypokalemia, hypersensitivity to polystyrene sulfonate resins, obstructive bowel disease, neonates with reduced gut motility, oral administration in neonates
- Administration: Oral and rectal (enema)
- Available as powder, suspension, enema
- Store at 25° C (77° F)
- Average daily adult dose of resin: 15 g to 60 g
- Administer 15 g 1 to 4 times daily
- Cost: 454 gram jar is \$50-\$150



US Food and Drug Administration [website]. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=011287>. Accessed May 14, 2018. Elliott W, et al. Relias [website]. Pharmacology update. Patiomer for oral suspension (veltassa). <https://www.ahcmedia.com/articles/137411-patiomer-for-oral-suspension-veltassa>. Accessed May 14, 2018.

## SPS: The Issues List

- No rigorous clinical trials to determine efficacy and safety
- Takes several hours for reduction in serum potassium
- Questionable utility in emergent hyperkalemia
- Questionable efficacy when not combined with sorbitol
- Questionable safety concerns
- Drug interactions
- Mixing, dosing, and palatability

Batterink J, et al. *Can J Hosp Pharm*. 2015;68(4):296-303.

## SPS Clinical Trial Data

- Approval based on study of 32 patients
  - Hyperkalemia, azotemia, hemodialysis not yet available
  - Serum potassium decreased by 0.9 mEq/L in 24 hours
- Retrospective analysis of 157 patients
  - Mean serum potassium, 5.9 mEq/L
  - Reduction of 0.7-1.1 mEq/L
- Most often combined with sorbitol
- ClinicalTrials.gov identifier NCT01866709: Safety and efficacy of SPS in hyperkalemia
  - Prematurely terminated for safety reasons due to high frequency of adverse events in SPS group

Flinn RB, et al. *N Engl J Med*. 1961;264:111-115. Batterink J, et al. *Can J Hosp Pharm*. 2015;68(4):296-303. Scherr L, et al. *N Engl J Med*. 1961;264:115-119. ClinicalTrials.gov [website]. <https://clinicaltrials.gov/ct2/show/NCT01866709?term=sodium+polystyrene+sulfonate&rank=2>. Accessed May 14, 2018.

## SPS Clinical Trial Data

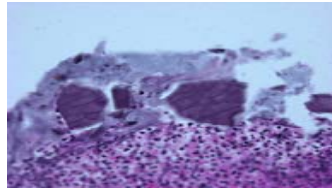
- Prospective, randomized, single-blind trial
  - 97 patients with CKD, treated with SPS for 3 days
  - Significant reduction in serum potassium
  - Significant rate of adverse effects (GI, increasing BP)
- Prospective, randomized, double-blind, placebo-controlled trial
  - 33 patients with CKD (mean eGFR ~20 mL/min/1.73 m<sup>2</sup>; mean potassium ~5.2 mEq/L)
  - Short duration (7 days)
  - SPS greater reduction in serum potassium
  - Increased rate of adverse effects
  - Small sample size

Nasir K, et al. *J Ayub Med Coll Abbottabad*. 2014;26(4):455-458. Lepage L, et al. *Clin J Am Soc Nephrol*. 2015;10(12):2136-2142.



## Incidence of Colonic Necrosis

- Retrospective study (n=752)
  - 0.3% overall incidence
  - No cases in control group (n=862)
- Retrospective cohort
  - 0.14% vs 0.07%
  - Preparation with 33% sorbitol
- Systematic review
  - 30 reports (58 cases)
    - 41 preparations with sorbitol
    - 17 preparations without sorbitol
- Retrospective chart review
  - 0.4% overall incidence



Gerstman BB, et al. *Am J Kid Dis.* 1992;20:159-161. Watson MA, et al. *Am J Kid Dis.* 2012;60:409-416. Harel Z, et al. *Am J Med.* 2013;126(3):264.e9-264.e24. Hagan AE, et al. *Clin Nephrol.* 2016;85:38-43.

## SPS Drug Interactions

**FDA Drug Safety Communication: FDA requires drug interaction studies with potassium-lowering drug |**  
(sodium polystyrene sulfonate)

- Prescribers and patients should consider separating SPS dosing from other medications taken by mouth by at least 6 hours
  - Reduction in quetiapine levels
  - Reduction in lithium absorption
  - Reduction in iron absorption

Hoge RH, et al. *J Clin Pharm Ther.* 2015;40(3):355-357. O'Connor TA, et al. *Ann Emerg Med.* 1996;28(5):504-507. US Food and Drug Administration (FDA) [website]. Drugs@FDA: FDA approved drug products. <https://www.fda.gov/Drugs/DrugSafety/ucm468035.htm>. Accessed May 18, 2018.

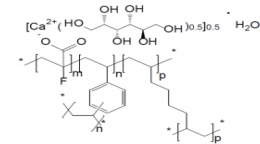
A patient is prescribed patiomer and asks about how long the product can be left out of a refrigerated environment. What is your response?

- A. 1 week
- B. 1 month
- C. 3 months
- D. Requires refrigeration



## Organic Polymer Resin Patiomer Calcium Sorbitex (Patiomer; RLY5016)

- Potassium exchange resin
- Non-absorbed, non-degradable
- Primary effect in colon
- Powder packets
  - Specific instructions on preparing dose at home
  - Must be refrigerated, stable for 3 months at room temperature
  - Take with or without food
- Available as
  - 8.4 g, 16.8 g, 25.2 g powder packets
  - Once daily
  - Starting dose 8.4 g
  - Titrate weekly
  - Cost: \$>700 per 30 packets in community, prices lower for hospitals



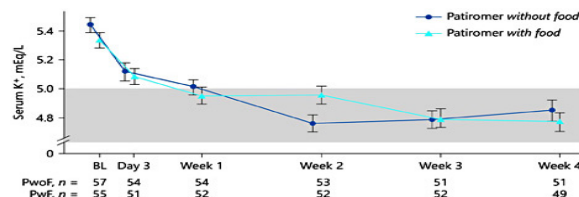
m = number of 2-fluoro-2-propenoate groups  
n, p = number of crosslinking groups  
H<sub>2</sub>O = associated water  
\* = indicates an extended polymeric network

m = 0.91  
n + p = 0.09

US Food and Drug Administration [website]. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=205739>. Accessed May 14, 2018.

## Organic Polymer Resin Patiromer Calcium Sorbitex (Patiromer; RLY5016)

### TOURMALINE Trial



- 87.3% of patiromer with food group and 82.5% of patiromer without food group achieved target potassium levels in the target range at either week 3 or week 4

Pergola PE, et al. *Am J Nephrol*. 2017;46:323-332. US Food and Drug Administration [website]. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=205739>. Accessed May 14, 2018.

## Patiromer Drug Interactions

- In vitro binding studies as part of FDA requirement
  - 28 drugs tested; 50% of drugs tested were bound by patiromer
  - Separate potential interacting drugs by 3 hours from patiromer

>50% Interaction	30%-50% Interaction	<30% Interaction
Amlodipine Cinacalcet Ciprofloxacin Levothyroxine Quinidine Trimethoprim	Clopidogrel Lithium Metoprolol Verapamil Warfarin	Allopurinol Amoxicillin Apixaban Aspirin Atorvastatin Cephalexin Digoxin Glipizide Lisinopril Phenytoin Rivaroxaban Spironolactone Valsartan

### Drugs Evaluated

Amlodipine  
Cinacalcet  
Ciprofloxacin  
Clopidogrel  
Furosemide  
Levothyroxine  
Lithium  
Metformin  
Metoprolol  
Trimethoprim  
Verapamil  
Warfarin

Department of Health and Human Services, Center for drug evaluation and research.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/205739Orig1s000RiskR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205739Orig1s000RiskR.pdf). Weir MR, et al. *Kidney Int*. 2016;90:696-704.

## Patiromer Clinical Trial Data

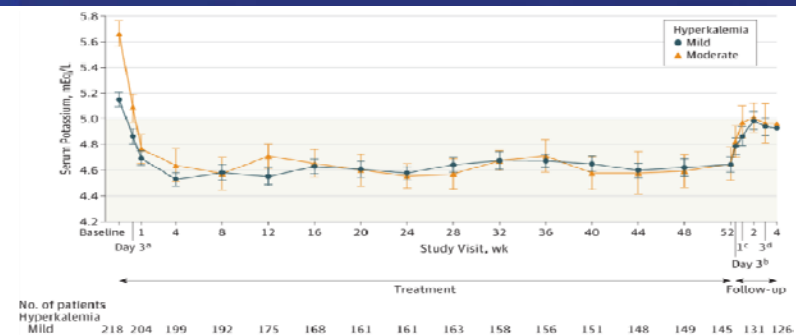
Trial	Comments	Results
AMETHYST-DN	<ul style="list-style-type: none"> <li>Dose finding, safety + efficacy</li> <li>Diabetes mellitus + CKD (stages 3 and 4)</li> <li>Hyperkalemic</li> <li>Receiving RAASI</li> <li>52 weeks</li> </ul>	<ul style="list-style-type: none"> <li>All patients on ACEI/ARB/combo</li> <li>Majority on spironolactone</li> <li>Effective for mild and moderate hyperkalemia</li> <li>Serum K maintained for 52 weeks; increased 3 days after discontinuation</li> </ul>
OPAL-HK	<ul style="list-style-type: none"> <li>Safety + efficacy</li> <li>CKD (stages 3 + 4)</li> <li>Hyperkalemic</li> <li>Receiving RAASI</li> <li>2 phases, 4 weeks + 8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>All patients on ACEI/ARB/combo</li> <li>Effective for mild/mod/severe hyperkalemia</li> <li>Constipation most common ADR (11%)</li> </ul>
PEARL-HF	<ul style="list-style-type: none"> <li>Safety, efficacy, tolerability</li> <li>Chronic HF</li> <li>Indication for spironolactone</li> <li>Hyperkalemic</li> <li>CKD + HF therapy (RAASI)</li> <li>4-week trial</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of hyperkalemia lower in treatment group</li> <li>Additional benefit seen in those with CKD and HF</li> <li>GI-related ADRs occurred in 21% of participants</li> </ul>

ADR = adverse drug reaction.

Bakris GL, et al. *JAMA*. 2015;314(2):151-161. Weir MR, et al. *N Engl J Med*. 2015;372:211-221.

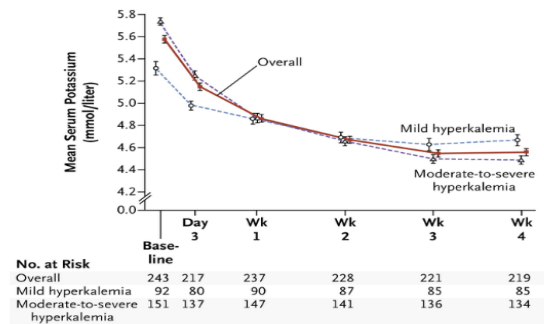
Pitt B, et al. *Eur Heart J*. 2011;32(7):820-828.

## AMETHYST-DN Trial: Serum Potassium Levels



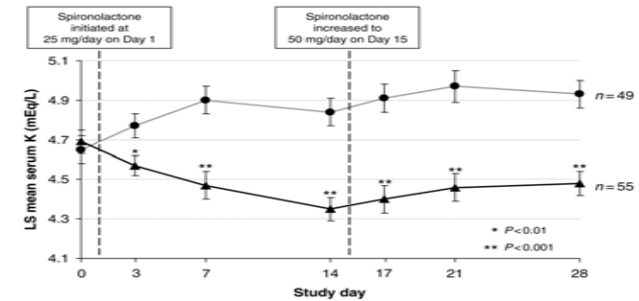
Bakris GL, et al. *JAMA*. 2015;314(2):151-161.

## OPAL-HK Trial: Serum Potassium Levels



Weir MR, et al. *N Engl J Med.* 2015;372:211-221.

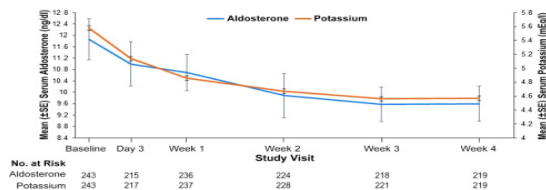
## PEARL-HF Trial: Serum Potassium Levels



Pitt B, et al. *Eur Heart J.* 2011;32(7):820-828.

## Additional Benefit of Patiromer

Measure	Mild Hyperkalemia	Mod/Severe Hyperkalemia	Overall
Serum aldosterone (ng/dL)	-1.81 ± 0.74	-3.19 ± 0.58	-2.50 ± 0.47
Systolic BP (mm Hg)	-5.40 ± 1.84	-5.57 ± 1.44	-5.48 ± 1.17
Diastolic BP (mm Hg)	-3.34 ± 1.21	-4.67 ± 0.95	-4.00 ± 0.77



Weir MR, et al. *Kidney Int.* 2016;90:696-704.

## Patiromer: The Issues List

- Takes several hours for reduction in serum potassium
  - Onset occurs in 7 hours, full effect in days
- Questionable utility in emergent hyperkalemia
- Electrolyte disorders
  - Hypokalemia; hypomagnesemia
- Drug interactions
  - Metformin, levothyroxine, ciprofloxacin are most notable
  - Separate by at least 3 hours
- High cost
- Specific storage, mixing, and administration

Pitt B, et al. *Expert Opin Drug Saf.* 2018;17(5):525-535.

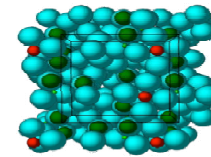
A prescriber calls to ask about patiromer dosing and titration. What is the starting dose?

- A. 8.4 g once daily
- B. 8.4 g twice daily
- C. 16.8 g once daily
- D. 16.8 g twice daily



## Update: FDA Approval of Sodium Zirconium Cyclosilicate (Formerly ZS-9)

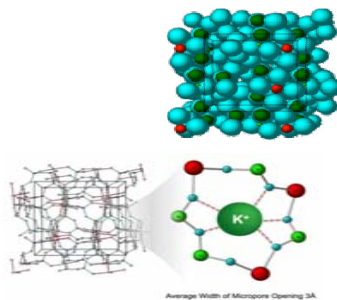
- May 21, 2018: FDA approves sodium zirconium cyclosilicate for oral suspension to treat adults with hyperkalemia
- Sodium zirconium cyclosilicate: Inorganic, non-absorbed, selective potassium ion trap



Stavros F, et al. *PLoS One*. 2014;9(12):e114686. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. Sodium zirconium cyclosilicate. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=20707>. Accessed August 7, 2018.

## Sodium Zirconium Cyclosilicate (Formerly ZS-9)

- Properties
  - Inorganic cation exchange resin
  - Non-absorbed, non-degradable
  - Crystalline lattice structure
  - Traps K<sup>+</sup> throughout intestine
  - Exchanges Na<sup>+</sup> and H<sup>+</sup> for K<sup>+</sup>
- Available forms
  - Powder for suspension
  - Tablet, dissolvable?



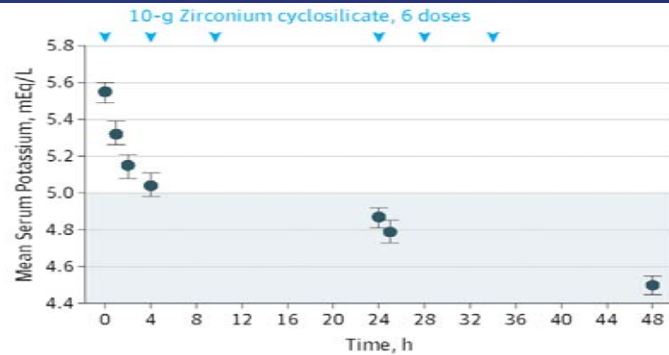
Stavros F, et al. *PLoS One*. 2014;9(12):e114686. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. Sodium zirconium cyclosilicate. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=20707>. Accessed August 7, 2018.

## HARMONIZE Trial

- Phase 3, randomized, double-blind, placebo-controlled trial
- Persistent hyperkalemia: Serum K<sup>+</sup> >5.1 mEq/L
- 48-hour open-label phase
- Those achieving normokalemia randomized to 28-day study
  - Randomized to placebo or 3 different ZS-9\* doses (5 g, 10 g, 15 g daily)
- 258 participants in initial 48-hour open-label phase
- 237 patients in 28-day study

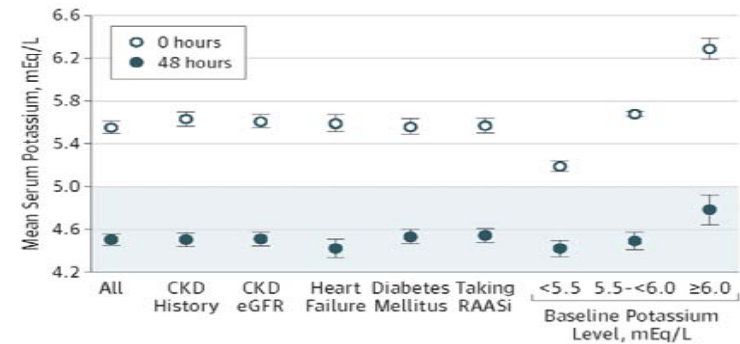
\*Former name of sodium zirconium cyclosilicate, which is now FDA approved.  
HARMONIZE = Hyperkalemia Randomized Intervention Multi-Dose ZS-9 Maintenance.  
Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233. Chaitman M, et al. *P&T*. 2016;41(1):43-50.

## HARMONIZE Trial



Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233.

## HARMONIZE Trial



Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233.

## HARMONIZE Trial

Adverse Effects	Open-Label Phase (10 g/d) N=258 No. (%)	Placebo N=85 No. (%)	ZS-9 <sup>†</sup> 5 g N=45 No. (%)	ZS-9 <sup>†</sup> 10 g N=51 No. (%)	ZS-9 <sup>†</sup> 15 g N=56 No. (%)
Any event	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)	25 (44.6)
Constipation	2 (0.8)	6 (7.1)	0	1 (2.0)	1 (1.8)
Edema*	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Hypokalemia	0	0	0	5 (9.8)	6 (10.7)

\*Including generalized and peripheral edema. <sup>†</sup>Former name of sodium zirconium cyclosilicate, which is now FDA approved.

Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233.

## ZS-9\* in Hyperkalemia Trial

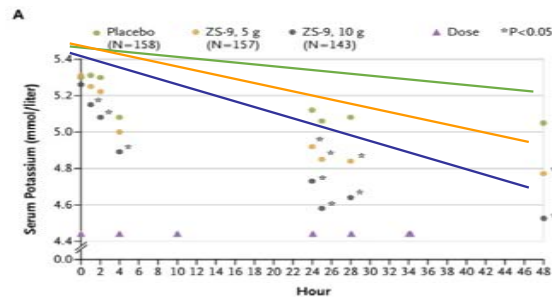
- Phase 3, randomized, two-stage, double-blind, placebo-controlled
- Stage 3 CKD
- Serum K, 5.0-6.5 mEq/L
- Dose-ranging study
- 753 patients randomized to receive ZS-9
  - 1.25 g, 2.5 g, 5 g, or 10 g
- 72% attained normal serum K
- Steepest decline in first 48 hours
- ADEs similar to those of placebo, primarily GI in nature

\*Former name of sodium zirconium cyclosilicate, which is now FDA approved.

ADE = adverse drug event.

Packham DK, et al. *New Engl J Med*. 2015;372:222-231.

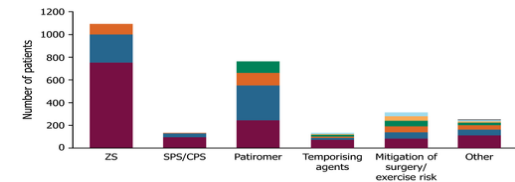
## ZS-9\* in Hyperkalemia Trial: Potassium Levels



\*Former name of sodium zirconium cyclosilicate, which is now FDA approved.  
Packham DK, et al. *New Engl J Med*. 2015;372:222-231.

## Integration of New Binders into Clinical Practice

- Requires some effort for coverage by insurers
- Availability of product limited to specialty pharmacies and select community pharmacies
- Use in hospitals dependent on budget and formulary decisions
- Patiromer requires specific storage, mixing, and administration considerations
  - Now may be taken with or without food
  - Counseling important



Note: Each bar represents a treatment or a treatment category, with different colors representing separate studies within that category.

Palaka E, et al. *Int J Clin Pract*. 2018;72(2):e13052. Evidence in support of hyperkalemia management strategies: A systematic literature review. 2018;72(2). First published January 30, 2018. doi: 10.1111/ijcp.13052. <http://www.4-traders.com/ASTRAZENECA-4000930/news/Study-Data-from-AstraZeneca-Update-Understanding-of-Hyperkalemia-Evidence-in-support-of-hyperkalem-25958595/>. Accessed May 14, 2018.

## The Pharmacist's Role in the Management of Hyperkalemia

- Identify patients at risk for drug-induced hyperkalemia and opportunities to manage chronic conditions when at risk for hyperkalemia
- Counsel patients to ensure they have sufficient understanding, knowledge, and skill to follow their pharmacotherapeutic regimens and monitoring plans
- Seek ways to motivate patients to learn about their treatment and to be active partners in their care
- Liaise with dietitian regarding patients' diets to assess for sources of potassium

American Society of Health-System Pharmacists. ASHP guidelines on pharmacist-conducted patient education and counseling. *Am J Health-Syst Pharm*. 1997; 54:431-434. Raymond CB. *Can J Hosp Pharm*. 2013;66(6):369-374. Raymond CB, et al. *CANNT J*. 2010;20(3):49-54.

## Lessons Learned

- SPS
  - Use limited by questionable efficacy and ADEs
- Patiromer
  - Effective for management of hyperkalemia
  - Use for emergency management of hyperkalemia not approved
  - ADEs are known and seem minimal
    - Primarily GI and hypomagnesemia
  - No serious ADEs
  - Low risk of drug-drug interactions with other oral medications
- Sodium zirconium cyclosilicate (formerly known as ZS-9)
  - Received FDA approval in May 2018 for the treatment of hyperkalemia in adults
  - No longer term studies
  - Appears effective for acute management

## Conclusions

- Hyperkalemia is a common complication in patients with:
  - CKD and AKI
  - Diabetes mellitus
  - CVD
- Certain medications, such as RAASi, increase the risk of hyperkalemia
- SPS has questionable efficacy and safety concerns
- Newer agents, such as patiomer and sodium zirconium cyclosilicate:
  - Are more selective for potassium
  - Provide once-daily dosing
  - Require prior authorization for coverage

## Questions?

Thank you for your attention!

## The Flu Stops Here: Enabling Pharmacists and Pharmacy Technicians to Join the Fight

ICHP Annual Meeting  
September 14, 2018  
Oakbrook Terrace, Illinois



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### Speakers

Michael D. Hogue, Pharm.D., FAPhA, FNAP  
Associate Dean and Professor  
Samford University College of Health Sciences  
Birmingham, Alabama

Dennis Williams, Pharm.D., BCPS  
Associate Professor  
UNC Eshelman School of Pharmacy  
Chapel Hill, North Carolina



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### Disclosures

- Michael Hogue discloses that he is on the speakers bureau for Pfizer, Inc., and has served as a consultant to GlaxoSmithKline and Sanofi Pasteur. Dr. Hogue has a research grant from Merck & Co., Inc.
- Dennis Williams discloses that his spouse is employed by GlaxoSmithKline

*All conflicts were resolved through peer review.*



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## Program Objectives

- Pharmacists
  - Assess data about the impact of influenza illness and vaccine effectiveness
  - Evaluate evidence regarding strategies to optimize vaccination rates for patients and health care workers
  - Propose factors to consider in product selection of influenza vaccines
  - Apply knowledge regarding influenza vaccine and antiviral therapies to clinical scenarios
- Pharmacy Technicians
  - Evaluate information regarding the impact of influenza and influenza vaccine on patient outcomes
  - Design strategies to improve knowledge and awareness regarding influenza and the vaccine
  - Propose pharmacy-based activities to optimize influenza vaccination rates



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## 2017-18 Influenza Season: A Review

- A particularly harsh season
- Activity detected in November and extending into March
- An influenza A strain (H3N2) was predominant, although influenza B was responsible for most cases late in the season
- Over 99% of all strains assessed were susceptible to neuraminidase inhibitor antiviral agents



MMWR 2018; 67(22): 634-642

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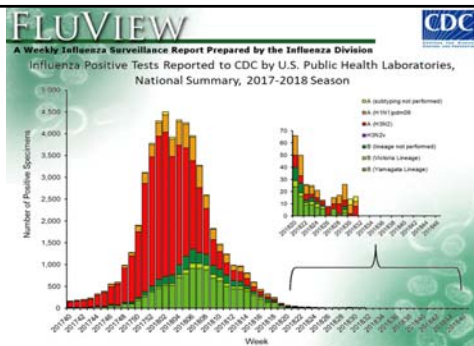
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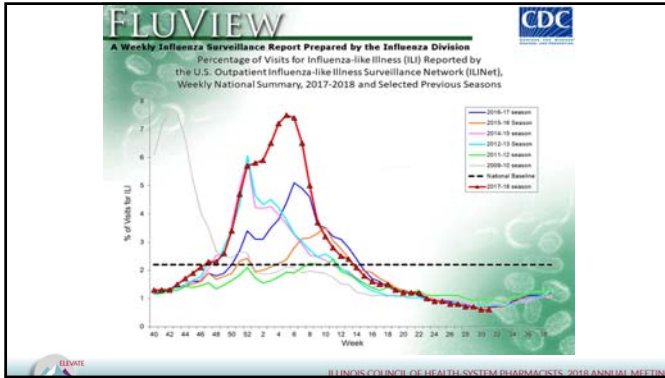
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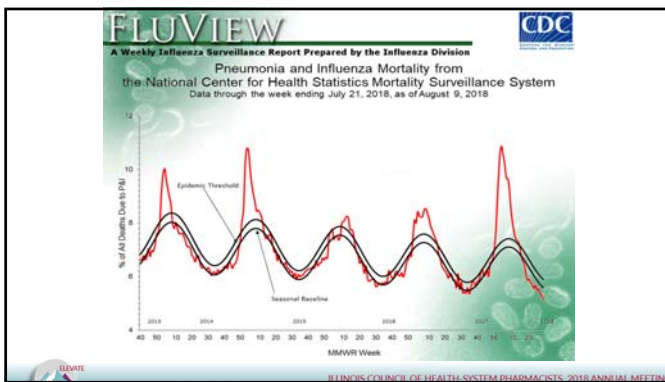
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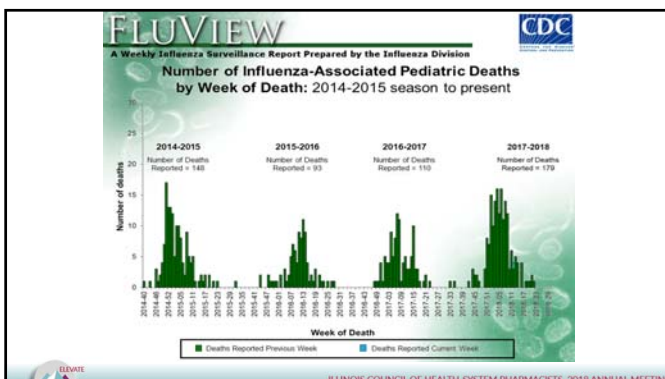
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## Influenza Vaccine: Supply and Vaccination Rates

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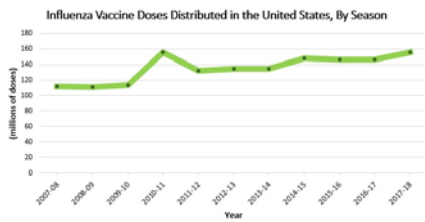
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### Influenza Vaccine Supply



<https://www.cdc.gov/flu/about/qa/vaxsupply.htm>

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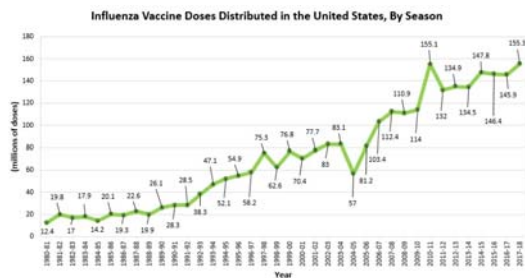
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<https://www.cdc.gov/flu/about/qa/vaxsupply.htm>

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## 2017-18 Influenza Vaccine Supply

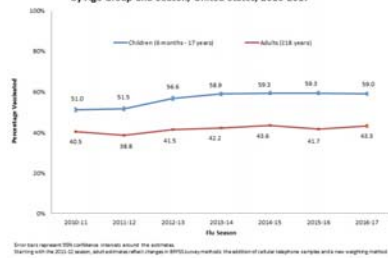
Estimated Supply 151-166 million

Thimerosal-free: 130 million

Quadrivalent: 119 million

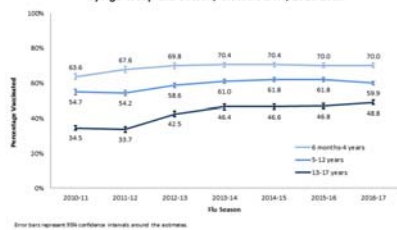
<https://www.cdc.gov/flu/about/qa/vaxsupply.htm>

Figure 1. Seasonal Flu Vaccination Coverage, by Age Group and Season, United States, 2010-2017



<https://www.cdc.gov/flu/fluview/coverage-1617estimates.htm>

Figure 2. Seasonal Flu Vaccination Coverage Among Children, by Age Group and Season, United States, 2010-2017



<https://www.cdc.gov/flu/fluview/coverage-1617estimates.htm>

Influenza Vaccine Coverage Rates for Persons 18 years of Age and Older, 2016-17

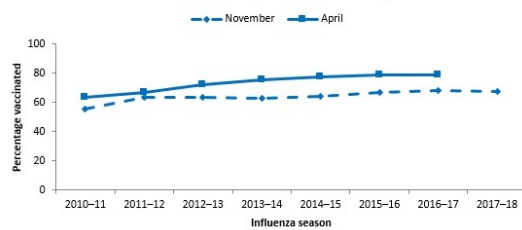
Age Group	Unweighted Sample Size	% <sup>1</sup> ± 95% CI <sup>1</sup>	Difference from the 2015-16 Season ± 95% CI
≥18 years	325,801	43.3 ± 0.6	1.6 ± 0.7 <sup>II</sup>
18-64 years	206,532	37.5 ± 0.6	1.2 ± 0.8 <sup>II</sup>
18-64 years with high risk conditions <sup>4</sup>	54,748	46.4 ± 1.2	0.4 ± 1.7
18-64 years without high risk conditions	149,533	34.9 ± 0.8	1.4 ± 1.0 <sup>II</sup>
18-49 years	107,527	33.6 ± 0.8	0.9 ± 1.1
18-49 years with high risk conditions	19,092	39.3 ± 1.8	-0.2 ± 2.7
18-49 years without high risk conditions	87,094	32.6 ± 0.8	1.1 ± 1.1
50-64 years	99,005	45.4 ± 1.0	1.8 ± 1.3 <sup>II</sup>
≥65 years	119,269	65.3 ± 1.0	1.9 ± 1.3 <sup>II</sup>

<https://www.cdc.gov/flu/fluview/coverage-1617estimates.htm>

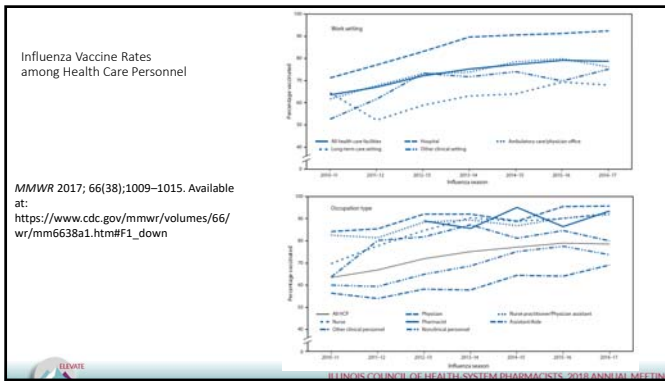
What is the Healthy People 2020 Goal for influenza vaccination rates among health care personnel?

- A. 50%
- B. 70%
- C. 80%
- D. 90%

Flu vaccination coverage among health care personnel vaccinated by November and by April for 2010-11 through 2016-17 flu seasons, and by November for 2017-18 flu season, Internet panel survey, United States



<https://www.cdc.gov/flu/fluview/hcp-ips-nov2017.htm>




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### 2017-18 Influenza Vaccination Rates for Health Care Personnel (Early Season Estimates)

- Overall, early-season rate for health care personnel was 67.6%
- Occupation:
  - Pharmacists 86.4%
  - Physicians 82.7%
  - Nurses 80.9%
  - NP/PA 79.7%
- Employment location:
  - Hospitals 82.6%
  - Ambulatory Clinics 68.7%
  - Long-term Care 58.5%
- Most common reasons for not receiving vaccine:
  - Fear of side effects or getting sick from vaccine 22.1%

<https://www.cdc.gov/flu/fluview/hcp-ips-nov2017.htm>

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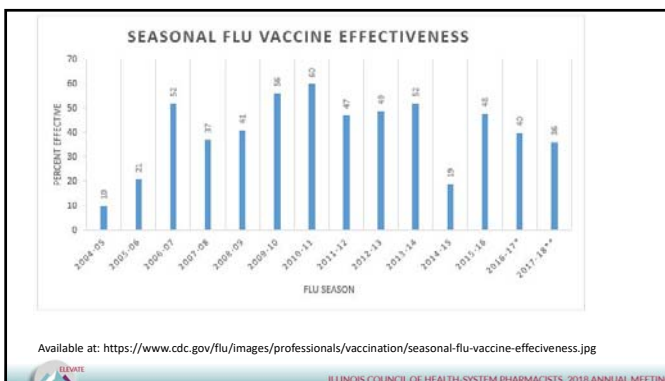
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## 2018-19 Influenza Vaccine Composition

### • Trivalent Vaccine

- A/Michigan/45/2015 A(H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus\*
- B/Colorado/06/2017-like (B/Victoria lineage) virus\*

### • Quadrivalent

- Above antigens, plus
- B/Phuket/3073/2013-like (B/Yamagata lineage) virus

\* Indicates new component for 2018-19 compared to 2017-18 Northern Hemisphere version

MMWR 2018; 67(22): 634-642



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## 2018-19 Influenza Vaccine Recommendation Highlights

- Vaccination with an influenza vaccine remains the most effective strategy to prevent influenza illness
- Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications
- Vaccination should be offered by the end of October if possible
- Some children aged 6 months through 8 years will require 2 doses
- Intranasal, live, attenuated influenza vaccine (LAIV4), which has not been recommended since the 2015-16 season, is an option for the 2018-19 influenza season
- No preference is expressed for any specific influenza vaccine product



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## Influenza Vaccine Effectiveness

Michael D. Hogue, Pharm.D., FAPhA, FNAP  
Associate Dean and Professor  
Samford University College of Health Sciences  
mdhogue@samford.edu



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Which of the following are independent effects of vaccination against influenza?

- A. "Herd" or community immunity against influenza
- B. Reduction in influenza-like illnesses ("The Flu")
- C. Lower risk of myocardial infarction in patients with CHD
- D. Reduced ICU admissions among people 65 years of age or older
- E. Each of the above



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## Acknowledgements

Vaccine Effectiveness Slides used in today's presentation were provided courtesy of:

- Daniel Jernigan, MD, MPH, Director, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC)



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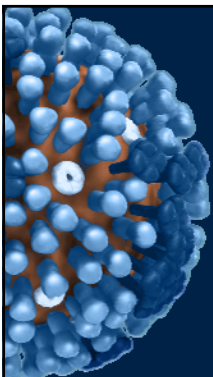
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Vaccine Effectiveness

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## Monitoring Influenza Vaccine Effectiveness Using Test-Negative Control Design (TND)

US Flu VE Network\*



Season	VE against A/B influenza viruses (95% CI)
2010-11	60% (53, 66)
2011-12	47% (36, 56)
2012-13	49% (43, 55)
2013-14	52% (44, 59)
2014-15	19% (10, 27)
2015-16	48% (41, 55)
2016-17	40% (32, 46)

## Preliminary adjusted vaccine effectiveness against medically attended influenza by age group 2017–18 for any influenza A or B virus infection

Any Influenza A or B virus	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Overall	1296/3097	(42)	2969/5538	(54)	38%	(32 to 43)	40%	(34 to 46)
Age group (yrs)								
6 mos-8	201/616	(33)	760/1380	(55)	60%	(52 to 68)	53%	(42 to 62)**
9-17	166/529	(31)	221/584	(38)	25%	(4 to 41)	29%	(8 to 46)
18-49	315/966	(33)	813/1893	(43)	36%	(24 to 45)	35%	(23 to 46)
50-64	301/571	(53)	583/938	(62)	32%	(16 to 45)	33%	(17 to 47)
≥65	313/415	(75)	592/743	(80)	22%	(-4 to 41)	20%	(-9 to 41)

\* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time. \*\* P-value < 0.001 for age group-VE interaction term compared to all other ages combined.

## Preliminary adjusted vaccine effectiveness against medically attended influenza A(H3N2) by age group, 2017–18

Influenza A(H3N2)	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Overall	813/1790	(45)	2969/5538	(54)	28%	(20 to 35)	24%	(15 to 33)
Age group (yrs)								
6 mos-8	131/337	(39)	760/1380	(55)	48%	(34 to 59)	37%	(17 to 52)**
9-17	118/335	(35)	221/584	(38)	11%	(-18 to 32)	10%	(-23 to 35)
18-49	218/581	(38)	813/1893	(43)	20%	(3 to 34)	14%	(-6 to 30)
50-64	166/298	(56)	583/938	(62)	23%	(0 to 41)	25%	(0 to 44)
≥65	180/239	(75)	592/743	(80)	22%	(-10 to 45)	17%	(-22 to 44)

\* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time. \*\* P-value = 0.05 for age group-VE interaction term compared to all other ages combined.

Preliminary adjusted vaccine effectiveness against medically attended influenza A(H1N1)pdm09 by age group, 2017–18

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
<b>Influenza A/H1N1pdm09</b>								
Overall	96/326	(29)	2969/5538	(54)	64%	(54 to 72)	65%	(55 to 73)
Age group (yrs)								
6 mos-17	26/154	(17)	981/1964	(50)	80%	(69 to 87)	82%	(71 to 88)
18-49	27/99	(27)	813/1893	(43)	50%	(22 to 68)	48%	(17 to 67)
50-64	18/40	(45)	583/938	(62)	50%	(6 to 74)	45%	(-6 to 72)
≥65	25/33	(76)	592/743	(80)	20%	(-80 to 65)	10%	(-116 to 63)

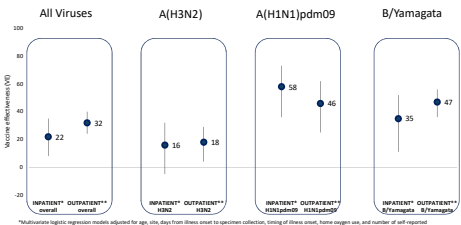
\* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.

Preliminary adjusted vaccine effectiveness against medically attended influenza B by age group, 2017–18

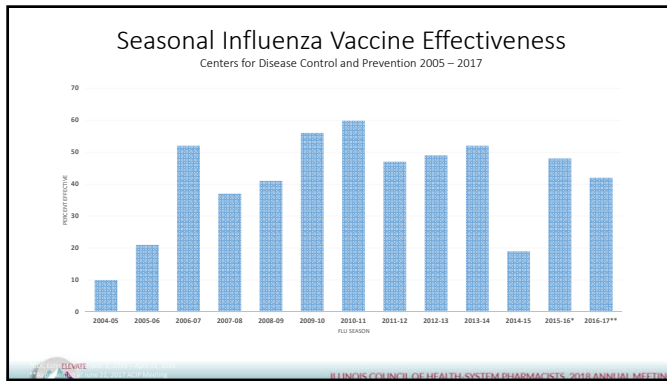
	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
<b>Influenza B/Yamagata</b>								
Overall	372/917	(41)	2969/5538	(54)	41%	(32 to 49)	49%	(40 to 56)
Age group (yrs)								
6 mos-8	44/130	(34)	760/1380	(55)	58%	(39 to 71)	46%	(19 to 64)
9-17	45/161	(28)	221/584	(38)	36%	(7 to 57)	39%	(9 to 59)
18-49	68/268	(25)	813/1893	(43)	55%	(40 to 66)	57%	(42 to 68)
50-64	108/216	(50)	583/938	(62)	39%	(18 to 55)	45%	(24 to 60)
≥65	107/142	(75)	592/743	(80)	22%	(-19 to 49)	29%	(-12 to 55)
<b>Influenza B/Victoria</b>								
Overall	8/39	(21)	2969/5538	(54)	78%	(51 to 90)		

\* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.

Preliminary VE estimates by virus type among inpatient and outpatient adults aged ≥18 years, 2017–18



\* Multivariable logistic regression models adjusted for age, site, days from illness onset to specimen collection, timing of illness onset, home oxygen use, and number of self-reported hospitalizations in the prior year.  
\*\* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.




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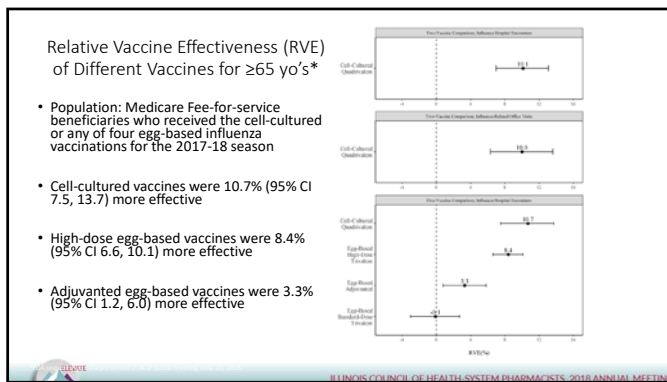
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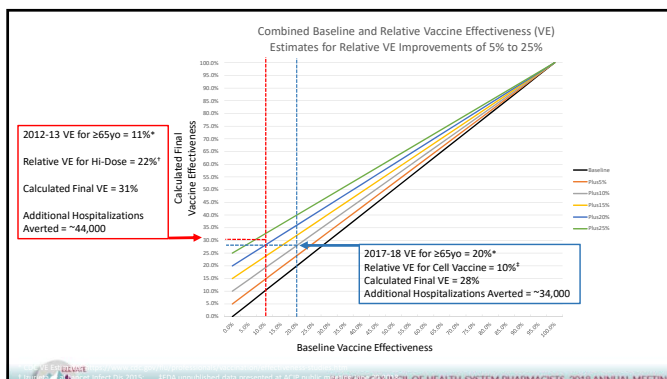
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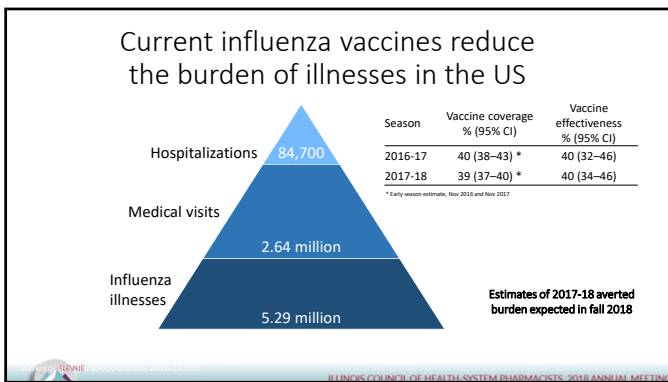
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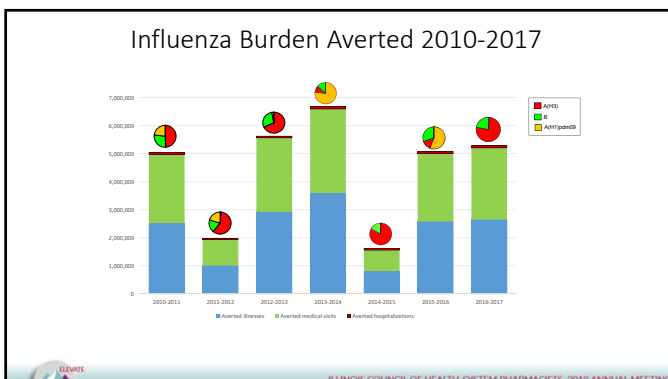
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## Attenuation of Disease

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## Data on Disease Attenuation

- Overall, data on attenuation comes from observational studies, most of which are only one season and often under-powered to adequately address attenuation of the spectrum of influenza disease
- Studies span the spectrum of association with prevention of severe disease to association with severe disease
  - Studies vary in age groups, seasons, study design
- Reported improved outcomes associated with vaccine include:
  - Death
  - ICU admission and duration
  - Hospital admission and duration
  - Fever
  - Combined symptom scores
  - Lower respiratory tract illness

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*Clinical Infectious Diseases*  
**MAJOR ARTICLE**

**Influenza Vaccination Modifies Disease Severity Among Community-dwelling Adults Hospitalized With Influenza**

Coranne Arendts,<sup>1</sup> Debbie Song,<sup>2</sup> Tracy J. Anderson,<sup>1,3</sup> Patricia A. Ryan,<sup>4</sup> Andrew George,<sup>5</sup> Shelley M. Zaritsky,<sup>6</sup> Nancy Brumm,<sup>7</sup> Andrew Kung'u,<sup>8</sup> William Bergman,<sup>9</sup> Tara Miller,<sup>10</sup> Anthony Robert Haines,<sup>11</sup> Lyle Sherry,<sup>12</sup> Steven B. Kohn,<sup>13</sup> Ruth Lippert,<sup>14</sup> Amy Thomas,<sup>15</sup> Mary Lou Lindgren,<sup>16</sup> William Schaffner,<sup>17</sup> Alicia M. Hay,<sup>18</sup> and Sandra D. Olsen<sup>19</sup>

- Study conducted through CDC hospitalization surveillance (FluSurvNet) in 2013-14 H1N1 season with overall VE for all ages = 52%
- Data for 4,910 hospitalized aged ≥18 yo
  - ~1/3 each for ≥18, 50-64, ≥65 yo
- Excluded institutionalized persons and those not treated with antiviral drugs since >80% had received oseltamivir
- Used Propensity Score Matching to address bias
- Prior similar study in 2012-13 H3N2 season found no significant findings

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### Vaccine Had Statistically Significant Impact in 2013-14

Ariola et al CID 2018

- Reduction in in-hospital death
  - 79% in 18-49 yo
  - 52% in 50-64 yo
  - 61% in ≥65 yo
- Reduction in ICU admissions
  - 37% in 18-49 yo
  - 37% in ≥65 yo
- Earlier discharge from ICU
  - 32% in 50-64 yo
  - 36% in ≥65 yo
- Earlier discharge from hospital
  - 13% in 50-64 yo
  - 24% in ≥65 yo

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### Selected Studies on Disease Attenuation

- VE against hospitalization in ≥65yo = 43% (22-59%), higher against ICU admission (70%) and death (76%) (Andrew 2017)
- VE against severe disease in ≥65yo = 43% (2-67%) (Casado 2016)
- VE against severe disease in all ages = 58% (20-88%) (Castilla 2013)
- VE no different in- vs outpatient over six seasons in all ages (Castilla 2018)
- Milder disease among vaccinated individuals infected with H3N2 viruses during the 2009-2014 seasons (Deiss 2015)
- VE no different in- vs out-patient over six seasons (Feng 2016)
- Reduction of 80% of lower respiratory tract illness and 70% of temperature above 39C in RCT of 3-8yo (Jain 2013)
- Vaccine associated with worse outcomes in 70 VA patients (Joshi 2015)
- No association between influenza vaccination and a reduction in the risk of hospital admission for ≥20 yos at Marshfield Clinic (McLean 2013)
- Vaccine reduced hospitalization and pneumonia in nursing home patients (Patriarca 1985)
- VE higher among inpatients (Petrie 2016)
- Vaccine associated with shorter duration of fever in elderly (Ruben 1974)
- No association between influenza vaccination and a reduction in the risk of hospital admission in influenza-confirmed patients (Van Wormer 2014)

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### The Tale of Two "Influenzas"? (Not really)

Walter is a 75 year old man, active and independent in his community

- Closely follows a healthy diet and exercises daily
- Because he is healthy, he refuses flu vaccine because he doesn't see the need
- Dies from influenza illness contracted on a cruise ship.

Joe is also a 75 year old man, active and independent in his community

- Follows a healthy diet, has a history of CVD & diabetes, does not exercise daily
- Receives annual flu vaccination
- Develops medically attended influenza while on a cruise ship; survives

Courtesy, Dr. McElhaney, 2018.

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### Case Scenario: Influenza Outcomes

Ann is 53 years old with Type 2 Diabetes and chronic lung disease (previously a smoker)

- Admitted to hospital with influenza, transferred to ICU and required intubation.
- Prior to influenza illness, diabetes and lung disease were well controlled and stable on medications.
- During ICU stay, experienced acute confusion for 2 days.
- Upon discharge home, experienced permanent loss of independence in activities of daily living due to physical limitations as a result of influenza.
- She had not been vaccinated in the current season, nor had anyone in her household.

Courtesy, Dr. McElhane. 2018.



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### At Your Tables, Discuss:

- What were Anne's risk factors for poor outcomes from influenza infection?
- Why is influenza such a "bad" infection in patients like Anne?
- What data, if any, tells us whether or not flu vaccine would have prevented Anne's situation?
- Is Anne's situation of long term loss of independence following influenza infection unusual?
- What antivirals would have been optimal during her hospitalization?
- What preventive steps should have been taken to reduce risk of household contacts from developing influenza illness?



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Select groups for report



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How long does the increased risk for mortality persist for a patient with cardiovascular disease who develops acute influenza?

- A. During hospitalization only
- B. 7 days post discharge
- C. 30 days post discharge



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The impact of influenza goes well beyond the infection rates...

- Influenza has been shown to seriously exacerbate chronic health conditions, including asthma, COPD, and chronic heart disease.
- Infection triggers an inflammatory response, especially in the respiratory tract, which can lead to sepsis.
- Serious illness and death is most likely to occur in patients with underlying chronic disease and in patients over 65 years of age regardless of underlying condition.
- Myocarditis, encephalitis, myositis, and rhabdomyolysis are all serious, potential complications of the inflammatory response caused by influenza.



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## Influenza Vaccines

Michael D. Hogue, Pharm.D., FAPhA, FNAP  
Associate Dean and Professor  
Samford University College of Health Sciences  
mdhogue@samford.edu



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## Let's Review – Patients at Higher Risk of Medical Complications Due to Influenza

- all children aged 6 through 59 months;
- all persons aged ≥50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who are immunocompromised due to any cause (including immunosuppression caused by medications or by HIV infection);
- women who are or will be pregnant during the influenza season;
- children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- persons who are extremely obese (BMI ≥40).

MMWR. 2017;66(2):1-20.

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- persons who are extremely obese (BMI ≥40).

MMWR. 2017;66(2):1-20.

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## To put it in perspective...As of July 31, 2018

### ➤ 328,210,000 people in the United States

➤ 20,020,810 are younger than 5 years of age.

➤ 51,200,760 are older than 65 years of age.

- 10,000 people will celebrate their 65<sup>th</sup> birthday every day through 2030

### ➤ There are a lot of healthcare providers:

- 861,000 practicing physicians
- 3,853,000 active registered nurses
- 312,500 licensed pharmacists

[AAMC Workforce Report 2016.](#)  
[United States Census Bureau Website.](#) 2018.  
[National Nursing Workforce Survey 2015.](#)  
[U.S. Bureau of Labor and Statistics Website.](#) 2016.

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## Influenza Vaccine Formulations\* United States, 2018-19

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• <b>IIV4, Standard Dose</b> <ul style="list-style-type: none"> <li>• Fluarix (≥3 y.o.)</li> <li>• Flulaval (≥3 y.o.)</li> <li>• Fluzone (≥6 months)</li> </ul> </li> <li>• <b>cclIV4, Standard Dose</b> <ul style="list-style-type: none"> <li>• Flucelvax (≥4 y.o.)</li> </ul> </li> <li>• <b>RIV4</b> <ul style="list-style-type: none"> <li>• Flublok (≥18 y.o.)</li> </ul> </li> <li>• <b>LAIV4</b> <ul style="list-style-type: none"> <li>• FluMist (2 to 49 y.o.)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>IIV3, Standard Dose</b> <ul style="list-style-type: none"> <li>• Afluria (≥9 y.o.)</li> <li>• Fluvirin (≥4 y.o.)</li> </ul> </li> <li>• <b>alIV3, Standard Dose</b> <ul style="list-style-type: none"> <li>• Flud (≥65 y.o.)</li> </ul> </li> <li>• <b>IIV3, High Dose</b> <ul style="list-style-type: none"> <li>• Fluzone High-Dose (≥65 y.o.)</li> </ul> </li> </ul> |
|--|---|

IIV4, quadrivalent inactivated influenza vaccine; cclIV4, cell-cultured, quadrivalent inactivated influenza vaccine; RIV4, recombinant quadrivalent inactivated influenza vaccine; LAIV4, live, attenuated, quadrivalent influenza vaccine; IIV3, trivalent inactivated influenza vaccine; alIV3, adjuvanted trivalent inactivated influenza vaccine.  
\*Anticipated based upon FDA approvals and manufacturer websites

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## Case Scenario: Influenza Vaccine Inventory

You are in charge of inventory management for both inpatient and outpatient services in your health system. The infection control committee has decided to intensify its efforts to prevent influenza infection through vaccination of staff and patients. They've asked the pharmacy department to ensure adequate supply for a) inpatient utilization, b) staff immunization, and c) outpatient clinic and pharmacy utilization.

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## At your Tables, Discuss:

- How will you decide the quantity of vaccine to order?
- Which vaccine products for influenza should you order?
- When should you order flu vaccine for best pricing and priority shipping?
- If you were to receive limited quantities of influenza vaccine, how would you prioritize which patients/clinics receive vaccine supply first?
- A patient receiving influenza vaccine experiences the very rare occurrence of anaphylaxis. What federally mandated reporting of this event must occur?

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### Select groups for report

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At your institution, you received a limited supply of IIV4 in August and it is depleted in mid-September. You have IIV3 and are promised a new shipment of IIV4 in a month. What is an appropriate policy for patients now?

- A. Administer IIV3 to high risk patients now, and revaccinate them when the IIV4 supply arrives.
- B. Defer high risk patients until the new supply of IIV4 arrives
- C. Vaccinate all patients with the currently available vaccine until the new supply arrives.

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### Quadrivalent Live Attenuated Influenza Vaccine (LAIV4)

- Intranasal administration
- Licensed by FDA and recommended by ACIP from 2013-14 through 2015-16 years as appropriate for otherwise healthy children and adults ages 2 – 49 years.
- Retrospective data analysis showed low effectiveness against A(H1N1)pdm09-like viruses.
- ACIP withdrew their support of the vaccine, and recommended that it NOT be used for the 2016-17 and 2017-18 seasons.
- Manufacturer maintained licensure of the product, began conducting studies on alternate vaccine strains

MMWR. June 8, 2018; 67(22); 643-45.

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### LAIV4 – Replacement Strains of A(H1N1)

- Manufacturer conducted a shedding and immunogenicity study in 2017-18 (Not an effectiveness study)
- Replicative fitness of vaccine virus strains is a known issue in influenza vaccine production, particularly with egg-based products.
- A/Bolivia/H1N1 was the reduced effectiveness strain; tested using an A/Slovenia/H1N1
- A/Slovenia immune responses were similar to those seen with highly effective pre-pandemic LAIV H1N1 strain.
- A new strain selection process will be applied to all future LAIV strains

CDC. Results of randomized trial of a new H1N1 LAIV strain in US children. Presented to the Advisory Committee on Immunization Practices, February 21, 2018. Atlanta, GA: US Department of Health and Human Services, CDC, 2018.

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### LAIV4 – 2018-19 Season

- ACIP again recommends use of the LAIV4 as an option for age-appropriate vaccination.
  - Committee recognized that removal in LAIV4 as an option led to an approximately 2% decline in pediatric influenza immunization rates.
  - Immunogenicity and shedding data compelled the ACIP to offer as a means to improve coverage, especially in school-based settings.
- American Academy of Pediatrics has a differing recommendation:
  - Recommends parents have children immunized preferentially with the injectable vaccine; reserving LAIV4 as a last resort only if a child would not otherwise be vaccinated
    - "Recent history has shown the injected form of the vaccine to be more consistent in protecting against more strains of the flu virus."

MMWR. June 8, 2018; 67(22): 643-45.

American Academy of Pediatrics [Press Release](#). May 21, 2018.

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Which of the following individuals would NOT be a candidate for Live, attenuated influenza vaccine?

- 5-year-old health child
- 30-year-old healthy community pharmacist
- 25-year-old nurse working with patients on isolation precautions due to bone marrow transplant
- 12-year-old adolescent with ADHD diagnosis
- Any of these people

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## IIV3, High Dose

- Data from 1986-2002 shows that antibody response to standard dose influenza vaccine is substantially lower in persons  $\geq 65$  years of age compared to young adults (17-53% vs. 70-90%).
- HD Contains four times the HA antigen contained in standard dose.
  - (60 $\mu$ g vs 15 $\mu$ g HA)
- Licensed for use in 2009 based upon immunogenicity data.
- Manufacturer was required to provide FDA with efficacy data post-licensure.

Goodwin K, Viboud C, Simonsen L. Vaccine. 2006; 24(8):1159-69.

## IIV3 High Dose (HD) versus Standard Dose (SD)

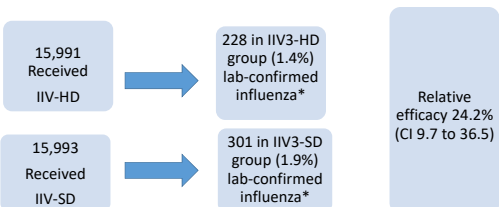
Regarding Immunogenicity:

Geometric mean titers were significantly higher in the HD vaccine	
A/H1N1	GMT 481.8 (457.7-507.1) for HD versus 271.8 (257.4-287.1) for SD
A/H3N2	GMT 685.5 (651.4-721.4) for HD versus 349.8 (332.1-368.6) for SD
B	GMT 138.1 (132.2-144.2) for HD versus 97.6 (93.3-102.0) for SD

N Engl J Med. 2014 Aug 14;371(7):635-45.

## IIV3 High Dose (HD) versus Standard Dose (SD)

31,989 Participants (126 North American Research Centers)



\*Includes Intention to Treat Analysis

N Engl J Med. 2014 Aug 14;371(7):635-45.

## What needs to be studied?

- Would HD influenza vaccine provide better vaccine effectiveness in immunocompromised patients?
  - At least one study suggests it might.
- If HD vaccine produces higher titers in older adults where the immune system is less responsive, wouldn't HD vaccine be better in younger adults or children?
  - Studies so far in younger populations have been inconclusive, but under-powered.

[Biol Blood Marrow Transplant](#), 2016 Mar;22(3):528-35.

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## Adverse Event Profile, IIV3 High Dose

**Table 1: Study 1<sup>a</sup>: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with Fluzone High-Dose or Fluzone, Adults 65 Years of Age and Older**

	Fluzone High-Dose (N <sup>b</sup> =2569-2572) Percentage			Fluzone (N <sup>b</sup> =1258-1260) Percentage		
	Any	Moderate <sup>c</sup>	Severe <sup>d</sup>	Any	Moderate <sup>c</sup>	Severe <sup>d</sup>
Injection-Site Pain	35.6	3.7	0.3	24.3	1.7	0.2
Injection-Site Erythema	14.9	1.9	1.8	10.8	0.8	0.6
Injection-Site Swelling	8.9	1.6	1.5	5.8	1.3	0.6
Myalgia	21.4	4.2	1.6	18.3	3.2	0.2
Malaise	18.0	4.7	1.6	14.0	3.7	0.6
Headache	16.8	3.1	1.1	14.4	2.5	0.3
Fever* (-99.5°F)	3.6	1.1	0.0	2.3	0.2	0.1

<sup>a</sup> NCT00910531 N is the number of vaccinated participants with available data for the events listed <sup>c</sup> Moderate: Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema and Injection-site swelling: ≥2.5 cm to <102.2°F; Myalgia, Malaise, and Headache: interferes with daily activities <sup>d</sup> Severe: Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema and Injection-site swelling: ≥5 cm; Fever: >102.2°F; Myalgia, Malaise, and Headache: prevents daily activities <sup>e</sup> Fever: The percentage of temperature measurements that were taken by oral route or not recorded were 97.8% and 2.2%, respectively, for Fluzone High-Dose and 98.6% and 1.4%, respectively, for Fluzone

Fluzone High-Dose Packing Insert. Sanofi Pasteur, Swiftwater, PA

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## Adjuvanted Vaccine (aIIV3)

- Contains a standard antigen load 15µg HA
- Contains MF-59<sup>®</sup> Adjuvant (Novartis)
  - Squalene-based oil-in-water emulsion
  - Practical: Product needs to be shaken before administration (suspension)
- Currently FDA-approved for use in individuals ≥ 65 years of age.
- Study complete and submitted to FDA for possible approval for use in children

[Vaccine](#), 2013 Dec 9;31(51):6122-8.

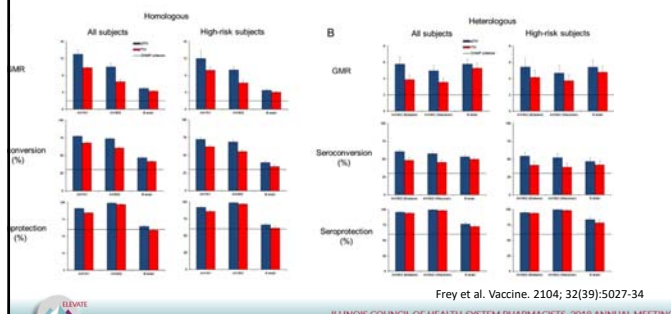
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## Immunogenicity of MF-59 Adjuvanted Flu Vaccine

- Randomized, observer-blinded trial comparing aIIV3 to IIV3.
  - U.S., Panama, Columbia, the Philippines
- Statistically powered to assess immunogenicity and seroconversion
  - Study was not powered adequately to show clinical effectiveness although authors did report effectiveness data.
- Equally matched groups of 3500 participants
  - Titers drawn at 22 days, 180 days, and 365 days post vaccination.
  - GMT of >2.0 above baseline considered adequate immunogenicity

Frey et al. Vaccine. 2104; 32(39):5027-34

## Immunogenicity



## Efficacy of MF-59 Adjuvanted Flu Vaccine in Patients $\geq 65$ Years of Age

- 11 studies enrolled 546,056 patients
  - 6 case control; 2 cohort; 2 prospective, community-based case control
  - Italy, Spain, Canada
  - 52.3% of all patients received aIIV3 (MF59)
- Authors conclude that available data over 20 years demonstrates VE at least as good as traditional IIV3;
  - May be some benefit over traditional IIV3 for A strain influenzas in particular

ILLUMINATE

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## Recombinant HA Flu Vaccine (rHIV3)

- Contains recombinant HA proteins to the three influenza viruses using insect cell lines for production of the vaccine
  - No eggs/egg protein
- Exact genetic match to reference strain; less potential for "drift"
- Expedited



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## Best Practices for Flu Vaccine



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## Key Resources for Every Clinician

- CDC Storage and Handling Toolkit
  - <https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/index.html>
  - Note: ALL persons with responsibility for vaccine supply should be required to view the 1-hour on-line module (1 C.E.U. is provided)
- CDC's Vaccine Administration Resources
  - <https://www.cdc.gov/vaccines/hcp/admin/admin-protocols.html>
  - Note: Especially important for all NEW employees administering vaccine
- Vaccine Adverse Event Reporting System
  - <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html>
  - Note: Recommend bookmarking this page on all in-house computers



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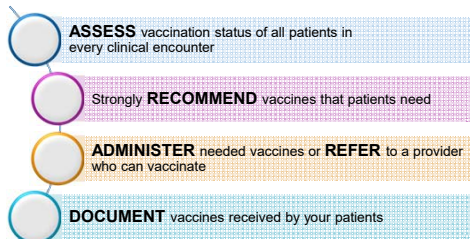
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## Standards for Adult Vaccination



Centers for Disease Control and Prevention. Standards for adult immunization practice: Overview. [cdc.gov/vaccines/hcp/patient-ed/adults/for-practice/standards/index.html](http://cdc.gov/vaccines/hcp/patient-ed/adults/for-practice/standards/index.html). Accessed 2/7/2017.

## Screening Patients Prior to Vaccination

- Represents an important component of the process of providing vaccine services
- Purpose is to identify patient's status to receive vaccine, identify possible precautions or contraindications, and determine other possible vaccines to administer

## Sample Screening Questions for Influenza Vaccine

- "How are you feeling today?"
  - The patient can receive vaccine unless you plan to refer them to another health professional now
- "What allergies do you have?"
  - Only relevant one for influenza would be serious egg allergy in which you might refer or be prepared to manage an allergic response
- "Have you ever experienced a serious adverse reaction to the influenza vaccine previously?"
  - Universal contraindication to any vaccine is a serious adverse reaction previously
- "What other medical conditions do you have?"
  - Helps to identify other vaccines to consider
- For live intranasal influenza vaccine
  - Are you pregnant?
  - Do you have any immunocompromising conditions or take immunosuppressive therapy?

The acronym, SIRVA, refers to:

- A. The reporting process for a patient experiencing an adverse reaction to a vaccine.
- B. The reporting process for a patient receiving the wrong vaccine.
- C. The procedures to follow for an allergic reaction.
- D. A possible shoulder injury related to improper vaccine administration.

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#### Shoulder Injury Related to Vaccine Administration (SIRVA)

- SIRVA is thought to result from the unintentional injection of a vaccine into tissues and structures lying underneath the deltoid muscle of the shoulder
- The Institute of Medicine (IOM) reviewed the scientific and medical literature finding that the evidence convincingly supported a causal relationship between vaccine administration and deltoid bursitis
- Atanasoff et al. published a case series reporting the experience of the Vaccine Injury Compensation Program with regard to shoulder injuries following vaccination. The IOM reviewed this article and commented that the cases were consistent with deltoid bursitis.

[www.hrsa.gov/advisorycommittees/childhoodvaccines/Meetings/20150604/sirva.pdf](http://www.hrsa.gov/advisorycommittees/childhoodvaccines/Meetings/20150604/sirva.pdf)

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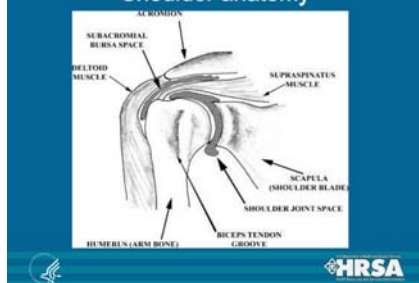
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#### Shoulder anatomy




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## Preventing SIRVA

- Follow CDC guidance for appropriate needle length selection<sup>1</sup>
- Ensure proper administration technique for intramuscular injections
  - Central portion of deltoid
  - Avoid the top 1/3 of the deltoid<sup>2</sup>
- Comprehensive, skills-based training should be integrated into existing staff education programs such as new staff orientation and annual education requirements<sup>1</sup>
- Persons administering vaccine should be in the same seated position as the patient. Avoid standing to administer vaccine to a patient who is seated.<sup>2</sup>

1. ACIP General Practice Recommendations. [www.cdc.gov/vaccines/imz/aciip/aciip-general-practice-recommendations.html](http://www.cdc.gov/vaccines/imz/aciip/aciip-general-practice-recommendations.html)  
 2. ACIP October 2017 Presentation of Dr. Andrew Kringer, CDC

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## Pharmacists and Pharmacy Technicians Need to be Vaccinated Too!

Immunization of HCW:  
 Recommendations of ACIP.  
 MMWR. 2011; 60(RR07):1-45.

Vaccines	Recommendations in brief
Hepatitis B	If you don't have documented evidence of a complete hepatitis B vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of HBV (1 dose now and the 2nd dose at least 28 days later). • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBc serologic tested 1-2 months after dose #3.
Flu (Influenza)	Get 1 dose of influenza vaccine annually.
MMR (Measles, Mumps, & Rubella)	If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to measles or mumps (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of MMR (1 dose now and the 2nd dose at least 28 days later). If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to rubella, only 1 dose of MMR is recommended. However, you may end up receiving 2 doses, because the rubella component is in the combination vaccine with measles and mumps. For HCWs born before 1957, see the <a href="http://www.cdc.gov/aciip/recommendations">CDC/ACIP vaccine recommendations</a> .
Varicella (Chickenpox)	If you have not had chickenpox (varicella), if you haven't had varicella vaccine, or if you don't have an up-to-date blood test that shows you are immune to varicella (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of varicella vaccine, 4 weeks apart.
Tdap (Tetanus, Diphtheria, Pertussis)	Get a one-time dose of Tdap as soon as possible if you have not received Tdap previously (regardless of when previous dose of Td was received). Get Td boosters every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.
Meningococcal	Those who are routinely exposed to isolates of <i>N. meningitidis</i> should get one dose.

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## Technicians: How to Help Your Pharmacist

- Review patient ages when they pick up prescriptions – and alert the pharmacist to opportunities to immunize (e.g. zoster and pneumococcal)
- Alert the pharmacist when patient's conditions may warrant vaccination (many, many examples).
- Make positive statements to patients about vaccines.
- Ensure vaccines are stocked and available when patients need them – patients are unlikely to return.
- Set up re-call reminder systems to bring patients back for vaccines dosed in a series...and leverage across the health-system with other providers.
- Ensure your pharmacy is connected to the state's Immunization Information System (registry), and then use it!

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## Prevention of Influenza: Progress toward a Universal Vaccine

- Vaccination represents the primary strategy to reduce the morbidity and mortality associated with influenza infection
- Currently, annual vaccination is required with seasonal influenza vaccine products
- Research has been underway for several years to identify a longer-lasting vaccine candidate
- Several approaches have been explored by the National Institute of Allergy and Infectious Diseases (NIAID)
- In May 2018, enrollment began in a Phase 2 study for a universal vaccine



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## Dennis' Broccoli Stalk (or Stem) and Head Analogy for the Influenza Virus



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## Universal Influenza Vaccine Concepts

- The hemagglutinin protein on the outer surface of the influenza virus consists of a stem and a head
- The head region varies from season to season and is the target of current seasonal influenza vaccine
- The stem (stalk) region of the protein remains relatively unchanged and is a current target of research for a universal longer acting vaccine



[https://images.slideplayer.com/24/6946434/slides/slide\\_14.jpg](https://images.slideplayer.com/24/6946434/slides/slide_14.jpg)



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## Universal Influenza Vaccine Efforts

- A NIAID research focus is to develop an influenza vaccine that provides robust, long-lasting protection against multiple subtypes of influenza virus, which could eliminate the need for annual vaccination with a seasonal influenza vaccine
- According to NIAID, a universal vaccine should:
  - Be at least 75% effective
  - Protect against multiple strains of influenza virus
  - Provide protection that lasts at least one year
  - Be suitable for people of all ages

Erbelding EJ, et al. JID 2018;218: 347-354



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- Other Strategies for Managing and Preventing Influenza



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## Influenza Illness

- Uncomplicated: abrupt onset
  - Fever
  - Myalgia
  - Headache
  - Malaise
  - Cough
  - Sore throat
  - Rhinitis
- Typically resolves in 3 to 7 days with lingering cough and malaise
- Complications:
  - Viral pneumonia
  - Secondary bacterial pneumonia
  - URT infections
  - Sepsis
  - Febrile seizures
  - Less common: encephalopathy, myocarditis, myositis, Reye's syndrome
  - Populations at higher risk include young, elderly, and people with cardiac or pulmonary diseases



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## Laboratory Diagnosis

- Surveillance and diagnostic testing can aid clinical judgment/guide treatment
- 60-69% practitioners report testing
- Diagnosis tests include viral culture, serology, rapid antigen, RT-PCR, and immunofluorescence assays
- Selected rapid influenza diagnostic tests (RIDTs) approved in outpatient settings
  - Others require moderate complex lab

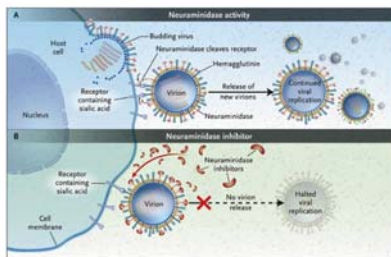
MMWR 2011 (Jan 21); 60 (1): No. RR-8

## Influenza Antiviral Agents for Treatment and Prevention of Influenza

- Neuraminidase inhibitors – active against Influenza A and B
  - Oseltamivir – oral (Tamiflu or generic)
  - Zanamivir – inhaled (Relenza)
  - Peramivir – intravenous (Rapivab)
- Adamantanes – not currently recommended for use due to resistance risk of >99%
  - Amantadine
  - Rimantadine

[www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)

## Neuraminidase Inhibitors Mechanism of Action



From Moscona A. N Engl J Med 2005; 353: 1363-73.  
Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from NEJM, Massachusetts Medical Society

Antiviral Agent	Treatment or Prophylaxis	Eligible Patient Age	Not Recommended In	Common Adverse Reactions Reported
Oseltamivir (oral)	Both	Tx: any age PPx: 3 months or older		Nausea, vomiting, headache. Some reports of dermatologic reactions and neuropsychiatric events
Zanamivir (Inhaled)	Both	Tx: 7 years and older PPx: 5 years and older	Underlying respiratory disease (e.g., asthma or COPD); or hospitalized patients	Oropharyngeal or facial edema, skin rash, bronchospasm, sinusitis, dizziness. Some reports of neuropsychiatric events
Peramivir (Intravenous)	Treatment	2 years and older		Diarrhea. Some reports of dermatologic reactions and neuropsychiatric events

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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## Treatment with Antiviral Therapies

- Initiate as soon as possible when influenza is suspected or confirmed and patient: (preferred within 48 hours of illness onset)
  - Is hospitalized
  - Has severe, complicated or progressive disease
  - Is at higher risk for complications
- High risk include young (less than 2 years), 65 years and older, immunosuppressed, or chronic pulmonary, cardiac, renal, hepatic, metabolic, or neurologic disorders
- High risk also includes pregnancy, American Indians, and residents in LTC
- Can be used in previously healthy, symptomatic outpatients, based on clinical judgement if within 48 hours of onset of symptoms
- Do not wait for laboratory confirmation to start therapy
- Treatment duration is 5 days for oral and inhaled therapy and one day for IV

MMWR 2011; 60(1): 1-25

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## Treatment with Antiviral Therapies

- Antivirals reduce symptoms by ~ 1 day if started within 48 hours of onset
- Reduces complications of pneumonia and death
- Treatment indicated for
  - People at risk for complications
  - People with moderate to severe disease
  - LTC residents who are ill during outbreak

MMWR 2011; 60(1): 1-25

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Antiviral Agent	Use and Duration	Child Dose	Adult Dose
Oseltamivir	Treatment (5 days)	<1 year old: 3mg/kg/dose twice daily One year or older: Weight based dosing ranging from 30 mg – 75 mg twice daily	75 mg twice daily
	Prophylaxis (7 days)	3 M-1 year: 3 mg/kg once daily One year and older: Weight based dosing ranging from 30 – 75 mg once daily	75 mg once daily
Zanamivir	Treatment (5 days)	7 years and older: 10 mg inhaled twice daily	10 mg (2 inhalations) twice daily
	Prophylaxis (7 days)	5 years and older: 10 mg inhaled once daily	10 mg (2 inhalations) once daily
Peramivir	Treatment (1 day)	2 to 12 years: 12 mg/kg/dose up to 600 mg once	600 mg once by IV infusion over at least 15 minutes (over 13 years of age)

Longer treatment durations may be used based on severity;  
Oseltamivir and Peramivir are dose-adjusted in renal dysfunction  
MMWR 2011; 60(1): 1-25

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## Pre and Post Exposure Prophylaxis with Antiviral Therapies

- Although antivirals are 70 to 90% effective in preventing influenza illness when used prophylactically, their use is not routinely recommended, except in institutional outbreaks (e.g., LTC facilities)
- When prophylaxis is used for known exposure, should be started within 48 hours
- Consideration can be given to:
  - People at high risk for complications who received influenza vaccine within the past two weeks (or not at all)
  - People with immunocompromising conditions or on immunosuppressive therapies
- Duration for known exposure is 1 week; with outbreak, duration is at least 2 weeks, and one week longer than last documented case

[www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)

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## Drug-Specific Considerations

- Can be used in pregnancy (but Category C)
- For decreased renal function (CrCl 10-30) reduce oseltamivir by half for both Tx and prophylaxis
- Safety
  - Zanamivir-avoided in respiratory/cardiac disease
  - Oseltamivir- GI in 10%; Neuropsychiatric events reported
- Drug interactions not a major concern

MMWR 2011 (Jan 21); 60 (1): No. RR-8

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## Renal Dosing Adjustment Recommendations from CDC

Antiviral Agent	CrCl Estimate	Treatment Dose	Prophylaxis Dose
Oseltamivir	61 to 90 ml/min	75 mg twice daily	75 mg once daily
	31 to 60 ml/min	30 mg twice daily	30 mg once daily
	11 to 30 ml/min	30 mg once daily	30 mg every other day
	Dialysis	30 mg after dialysis session (varies)	30 mg weekly after dialysis (varies)
Peramivir	Greater than 50 ml/min	600 mg once	
	30 to 49 ml/min	200 mg once	
	10 to 29 ml/min	100 mg once	
	Dialysis	Based on CrCl	

[www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)



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## Case Scenario: Acute Influenza

- Review Sally Smith case
- SS is a 73 year old woman with new onset of fever, muscle aches and respiratory symptoms
- On presentation, she is mildly dehydrated and hypoxemia
- She is admitted for fluids and observation



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## At your Table, Discuss:

- What pharmacotherapy recommendations do you have for Sally Smith
  - When should it be started, if at all?
  - What regimen is appropriate?
  - What are the goals for her management?
- Should this patient receive an influenza vaccine now?
- Assuming that her children and grandchildren are healthy and without symptoms, what should be recommended?



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## Select groups for report

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Should Sally Smith receive an influenza vaccine now?

- A. Yes, at discharge
- B. Yes, at least 48 hours after completing antiviral therapy
- C. No, not until next year

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## Summary

- An annual epidemic of influenza occurs annually and is associated with excess morbidity and mortality
- Currently, annual vaccination with seasonal influenza vaccine is the primary strategy to reduce problems associated with influenza
- Proper storage, handling, and administration of influenza vaccine is imperative to ensure that maximum effectiveness is achieved
- Health care personnel can educate, advocate, and provide vaccination services to reduce the risk and complications associated with influenza
- Antiviral therapies have a role when acute influenza infection is present or during outbreaks

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**The Flu Stops Here: Enabling Pharmacists and Pharmacy Technicians to Join the Fight**  
**Illinois Council of Health System Pharmacists**  
**September 14, 2018**

**Scenario One: Impact of Influenza Illness**

Ann is 53 years old with Type 2 Diabetes and chronic lung disease (previously a smoker)

- Admitted to hospital with influenza, transferred to ICU and required intubation.
- Prior to influenza illness, diabetes and lung disease were well controlled and stable on medications.
- During ICU stay, experienced acute confusion for 2 days.
- Upon discharge home, experienced permanent loss of independence in activities of daily living due to physical limitations as a result of influenza.
- She had not been vaccinated in the current season, nor had anyone in her household.

**Scenario Two: Vaccine Inventory**

You are in charge of inventory management for both inpatient and outpatient services in your health system. The infection control committee has decided to intensify its efforts to prevent influenza infection through vaccination of staff and patients. They've asked the pharmacy department to ensure adequate supply for a) inpatient utilization, b) staff immunization, and c) outpatient clinic and pharmacy utilization.

**Scenario Three: Acute influenza infection**

CC: "I just don't feel well. I am so tired and my whole body aches. I keep having chills and I had a fever this morning"

HPI: Sally Smith is a 73 year old female who presented to her primary care physician with complaints of increasing fatigue and generalized muscle ache for the past 24 hours. She states that she started with a sore throat, cough and runny nose two days prior. Her worsening symptoms prompted her to come to the clinic today.

ROS: General symptoms as noted above. Patient also endorses intermittent nausea, and she experienced diarrhea earlier today

PMH: Patient has a relatively unremarkable medical history except for hypertension and nasal allergies which began about 10 years ago.

SH and FH: Ms. Smith is a widow for 10 years. She lives with her son and family which includes two granddaughters, ages 18 months and 4 years. Family history is positive for breast cancer (mother) and hypertension (mother and siblings). She denies alcohol or illicit drug use, and stopped smoking 8 years ago (40 pack year history).

Meds: Amlodipine 10 mg daily; fluticasone nasal spray 50 mcg, each nostril daily.

Vaccines: Tdap 4 years ago, no vaccines since because of a concern for safety and fear of needles.

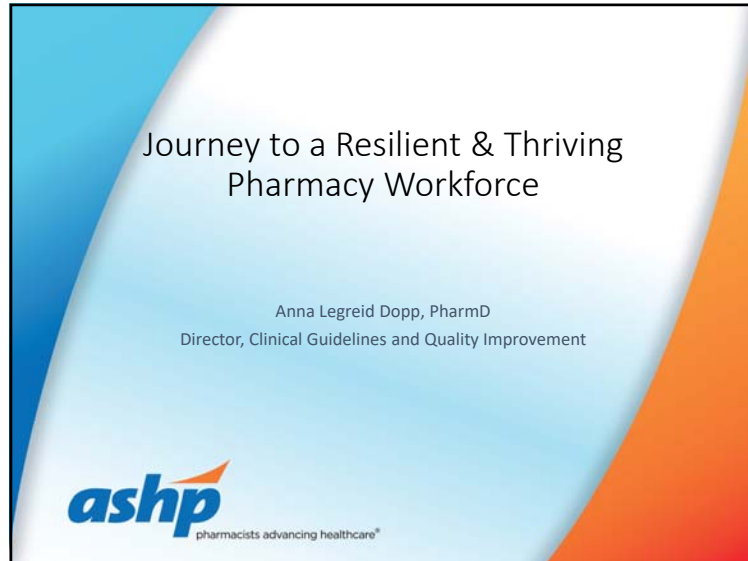
Allergies/ADR: ACE-I caused rise in creatinine, NKDA

PE: Hgt 68 inches, Wgt 64 kg, T: 38.5C BP 116/72, P 90, RR 19, O<sub>2</sub> sat 91%. Her skin is warm and mucous membranes are dry. A focused exam of her heart and abdomen was unremarkable. Lungs revealed crackles which cleared with coughing. She is A&O x3.

Labs: serum chemistry and hematology pending; one month ago, a baseline SCr was 1.5. A chest radiograph is unremarkable except for bibasilar atelectasis. Respiratory viral panel is also pending.

Assessment: possible influenza syndrome

Plan: Based on patient's hydration status and hypoxemia, will admit for fluids and observation while awaiting laboratory results.



## Disclosure

- No relevant financial relationship related to this continuing education activity
- No off-label uses of medications will be described in this presentation

## Outline

- Explain why clinician burnout is a patient care and healthcare workforce problem that needs addressing;
- Discuss what is known about burnout in the pharmacy workforce;
- Describe the National Academy of Medicine Clinician Well-Being and Resilience Action Collaborative; and
- Identify strategies to impact well-being and resilience in pharmacists, pharmacy residents, student pharmacists and pharmacy technicians.

## Engaged Workforce: What it is and what it isn't

### It is

- Emotional commitment to the organization
- Focus on mission and goals
- Discretionary effort
- ...the key to activating a high performing workforce

### It Isn't

- Employee happiness
- Employee satisfaction
- Zero burdens or stress



Forbes. What is employee engagement? Available at:  
<https://www.forbes.com/sites/kevinkruse/2012/06/22/employee-engagement-what-and-why/#2f96dd37f37>. Accessed August 14, 2018.

## Engagement: a Workforce Goal

"To win the marketplace you must first win the workplace"

~ Doug Conant, Former Campbell's Soup CEO

### Statistics:

- 70 % of U.S. employees report feeling unengaged
- In a study of engagement & burnout (n=1000)
  - Optimally engaged (40%): high engagement & low burnout
    - High resources (support, recognition), self-efficacy, low demands (low cumbersome bureaucracy), recovery from stress
  - Engaged-exhausted (20%): high engagement & high burnout
    - Simultaneous experiences of high engagement & burnout risk higher frustration and employee turnover

### Outcomes:

- Greater productivity, higher quality of work, increased safety, employee retention

Harvard Business Review. 1 in 5 highly engaged employees is at risk of burnout. February 2, 2018.

## Healthcare Workforce Burnout as a Patient Care Problem



Journal of the American Association of Nurse Practitioners

RESEARCH

Physical health, lifestyle beliefs and behaviors of entering graduate to support science

Harvard Business Review

**Burnout at Work Isn't Just About Exhaustion. It's Also About Loss**

by Emma S. June 28, 2017

VIEWPOINT

Addressing Physician Burnout: The Way Forward

Tait D. Shanafelt, MD, Mayo Clinic, Rochester, Minnesota.

Lotte N. Dyrbye, MD, MHPE, Mayo Clinic, Rochester, Minnesota.

Colin P. West, MD, PhD, Mayo Clinic, Rochester, Minnesota.

The US health care delivery system and the field of medicine have experienced tremendous change over the last decade. At the system level, narrowing of insurance networks, employed physicians, and financial pressures have resulted in greater expectations regarding productivity, increased workload, and reduced physician autonomy. Physicians also have to navigate a rapidly expanding medical knowledge base, more onerous maintenance of certification requirements, increased clerical burden associated with the introduction of electronic health records

PSNet

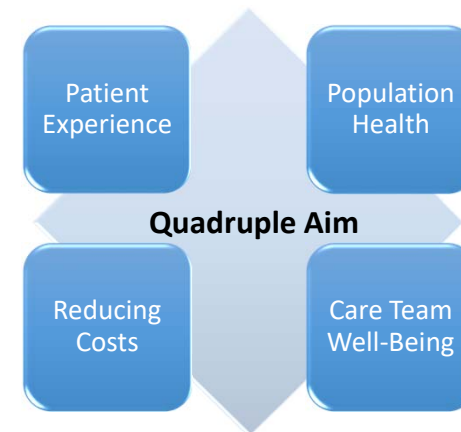
Home Topics Issues WebM&M Cases Perspectives

Perspectives on Safety February 2018

**Burnout Among Health Professionals: Effect on Patient Safety**

by Audrey London, PhD

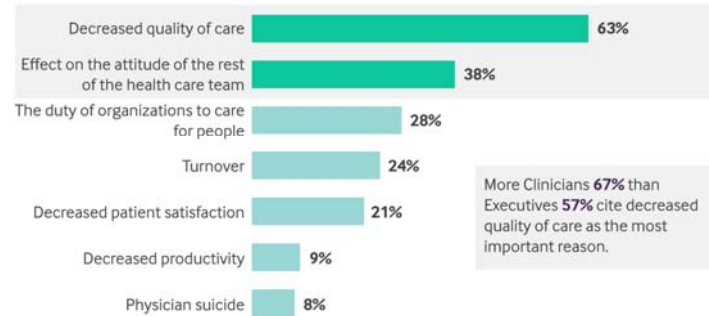
## From the Triple Aim to the Quadruple Aim



Bodenheimer T, Sinsky C. From triple aim to quadruple aim: care of the patient requires care of the provider. Ann Fam Med. 2014;12(6):573-6.

## Decreased Quality of Care Is the Top Reason to Address Physician Burnout

What are the top two most important reasons to address physician burnout?



Base = 570 (multiple responses)

Swensen S, Shanafelt, Mohta NS. Leadership survey: Why physician burnout is endemic, and how health care must respond. NEJM Catalyst. December 8, 2016. Available at: <https://catalyst.nejm.org/physician-burnout-endemic-healthcare-respond/>

## Burnout Medical Error

Bi-directional relationship

- Higher levels of burnout associated with increased odds of reporting a medical error in subsequent 3 months
- Self-perceived medical error associated with worsening burnout & depressive symptoms

Shanafelt Ann Surg 2009; Balch J Am Coll Surg 213; West JAMA 2006, 2009; Jones J Appl Psychol 1988; Cimiotti Am J Infect Control 2012; Welp Front Psychol 2015; Welp Crit Care 2016

## Burnout and Patient Safety: Summary of the Evidence

- Introduction: Evaluation of association between healthcare staff wellbeing, burnout, and patient safety
- Methods: Systematic Review
- Results: 46 studies included
  - Significant correlation between poor wellbeing in health care professionals and worse patient safety (n=16)
  - Significant association between burnout and patient safety (n=21)
- Conclusion: Studies show correlation between burnout and lower patient safety; more studies needed to determine causality

Hall LH, Johnson J, Watt I, et al. Healthcare staff wellbeing, burnout, and patient safety: A systematic review. PLoS ONE. 2016; 11(7): e0159015

## Health Care Costs

- |   |                   |
|---|-------------------|
| ↑Medical Errors   | ↑Absenteeism      |
| ↑Malpractice claims   | ↓Job productivity |
| ↑Turnover   | ↑Referrals        |
| <ul style="list-style-type: none"> <li>• 1.2-1.3 x salary (\$82-\$88,000 per RN in 2007)</li> <li>• \$500,000 to &gt;\$1 million</li> </ul> | ↑Ordering         |

Jones J Nurs Am 2008; Fibuch Physician Leadersh J 2015; Buchbinder Am J Manag Care 1999; Kushnir, Fam Pract 2014; Bachman Soc Sci Med 1999; Parker J Behav Med 1995; Toppinen-Tanner Behav Med 2005; Hilton J Occup Environ Med 2009

How have you seen burnout impact patient care?

## Burnout in the Pharmacy Workforce



## What is Stress?

- Stress is a physical, mental, or emotional factor that causes bodily or mental tension.
- Eustress is moderate or normal psychological stress considered to be beneficial for the experiencer
  - Motivates, focuses energy, is short-term, perceived as within our coping abilities, feels exciting, & improves performance
- Distress is extreme anxiety, sorrow, or pain
  - Can be short-or long-term, feels unpleasant, considered outside of our coping ability, decreases performance, may lead to mental & physical problems



<https://www.medicinenet.com/script/main/art.asp?articlekey=20104>

## A Careful Balance



## What is Burnout?

### • Syndrome of:

- Emotional exhaustion
- Depersonalization (e.g., cynicism)
- Low personal accomplishment



Maslach, C., S. E. Jackson, et al. (1996). Maslach Burnout Inventory Manual. Palo Alto, CA, Consulting Psychologists Press.

## Identify Burnout



### Valid and Reliable Survey Instruments to Measure Burnout

A key organizational strategy to improving clinician well-being is to measure it, develop and implement interventions, and then re-measure it. A variety of dimensions of clinician well-being can be measured including burnout, engagement, and professional satisfaction. Below is a summary of established tools to measure burnout. Each tool has advantages and disadvantages and some are more appropriate for specific populations or settings. This information is being provided by the [Research, Data, and Metrics Working Group](#) of the National Academy of Medicine [Action Collaborative on Clinician Well-Being and Resilience](#).

Click on each item for an overview of each valid and reliable instrument to measure burnout, self-being, and other work-related dimensions.

#### By group

► Maslach Burnout Inventory – Human Services Survey for Medical Personnel

► Oldenburg Inventory

► Physician Work-Life Study's Single-Item

► Copenhagen Burnout Inventory  
<https://nam.edu/valid-reliable-survey-instruments-measure-burnout-well-work-related-dimensions/>

#### Composite Well-Being

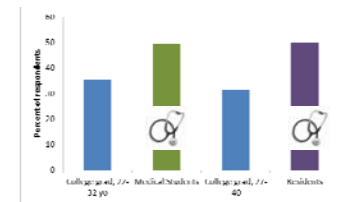
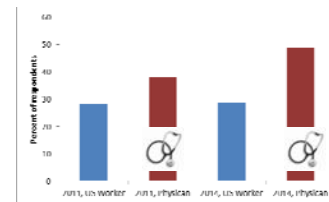
► Well-Being Index

## Maslach Burnout Inventory – Human Services Survey Tool

### • Medical Personnel

- Emotional exhaustion
  - Measures feelings of being emotionally overextended and exhausted by one's work
    - I feel emotionally drained from my work
- Depersonalization
  - Measures an unfeeling and impersonal response toward patients
    - I don't really care what happens to some patients
- Personal Accomplishment
  - Measures feelings of competence and successful achievement in one's work
    - I have accomplished many worthwhile things in this job
- Response options (frequency): never, a few times a year or less, once a month or less, a few times a month, once a week, a few times a week, every day

## High Prevalence of Burnout

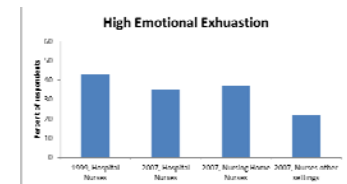


### Medicine

- 2014, 6880 physicians, all specialties, all practice types
- 2012, 5521 medical students & residents

### Nursing

- 1999, >10,000 inpatient RN
- 2007, 68,000 nurses



Aiken JAMA 2002;288; McHugh Health Aff 2011;30; Dyrbye Acad Med 89(3): 443-451; Shanafelt MCP 2015;90:1600



## Burnout: Pharmacy Residents

### Study Overview

- Stress and negative affect levels surveyed in PGY1 & PGY2s (n=524, 27.7% response)
- Those working > 60 hours/week reported higher levels of perceived stress and elevated depression, hostility, and dysphoria
- Perceived stress for pharmacy residents was  $19.06 \pm 5.9$ 
  - $14.2 \pm 6.2$  in 18-29 year old health adults
  - $20.3 \pm 7.4$  in cardiology medical residents

### Takeaways

- 10-item Perceived Stress Scale is a free, validated tool to assess stress among pharmacy residents
- Hostility was highest in PGY2
- When pressures of being overworked > resident's ability to cope, well-being is in danger

Le HM, Young SD. Evaluation of stress experienced by pharmacy residents. *AJHP*.2017;74:599-604

## Burnout: Clinical Pharmacists

- Jones and colleagues measured clinical pharmacist burnout (n=974)
  - Nearly ¾ included respondents are certified by BPS
  - More than half completed residency training
  - 61.2% overall burnout rate; 52.9% high emotional exhaustion
  - Characteristics of burned out clinical pharmacists:
    - Less likely to have children (p=0.002)
    - More likely to work more median hours (p<0.001)
    - More likely to have attained BPS certification (p=0.005)
  - No difference observed in practice area, hospital setting

Jones GM, Roe NM. Factors Associated With Burnout Among US Hospital Clinical Pharmacy Practitioners: Results of a Nationwide Pilot Survey. *Hosp Pharm*.2017;52:11:742-51.

## Drivers of Burnout in Healthcare Professionals

Risk Factors Associated With Burnout  
*Am J Health-Syst Pharm*. 2017; 74:e576-81

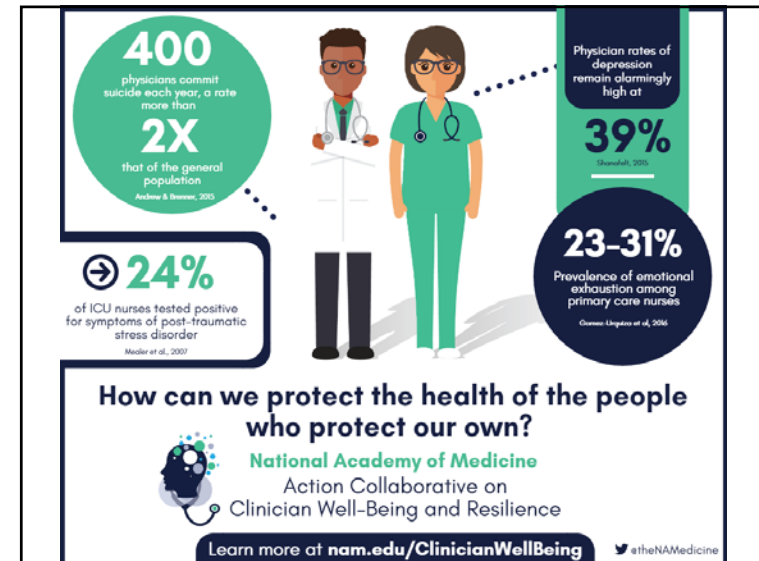
Risk Factor	Example
Workload	Job demands exceeding human limits; limited time to rest, recover, and restore.
Control	Role conflict; absence of direction in the workplace
Reward	Inadequate financial, institutional, or social reward in the workplace; lack of recognition
Community	Inadequate opportunity for quality social interaction at work; inadequate development of teams
Fairness	Perception of equity from an organization or leadership
Values	Organizational values are incongruous with an individual's personal values or beliefs
Job-person incongruity	Personality does not fit or is misaligned with job expectations and coping abilities

## National Academy of Medicine Action Collaborative Clinician Well-Being and Resilience



## National Academy of Sciences

- Founded in March, 1863
- Private, nonprofit organization of the country's leading researchers
- National Academy of Medicine
  - Formed in 1970 to advise the nation on medical & health issues
  - Dr. Victor Dzau is President



### PERSPECTIVE

COLLECTIVELY CONFRONTING THE CLINICIAN-BURNOUT CRISIS

## To Care Is Human — Collectively Confronting the Clinician-Burnout Crisis

Victor J. Dzau, M.D., Darrell G. Kirch, M.D., and Thomas J. Nasca, M.D.

*“Through collective action and targeted investment, we can not only reduce burnout and promote well-being, but also help clinicians carry out the sacred mission that drew them to the healing professions – providing the very best care to patients”*

Dzau VJ, Kirch DG, Nasca TJ. To care is human – collectively confronting the clinician-burnout crisis. NEJM.2018;378(4):312-314.

## Action Collaborative Goals

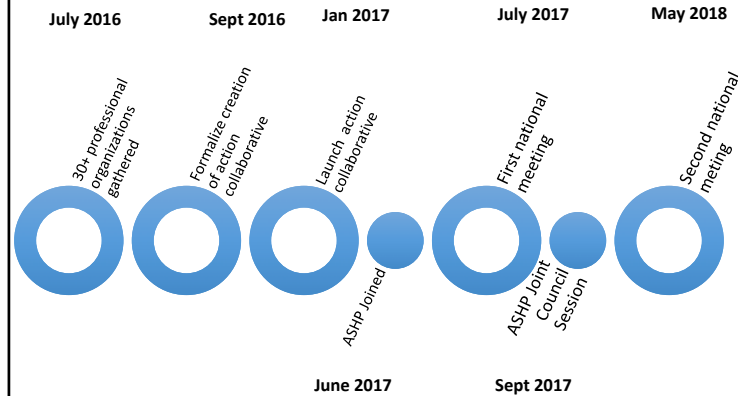
### NAM

- Improve baseline understanding across organizations of challenges to clinician well-being
- Raise visibility of clinician stress and burnout
- Advance evidence-based, multidisciplinary solutions to reverse these trends, leading to improvements in patient care by caring for the caregiver

### ASHP

- Improve patient outcomes through optimal medication use
- Identify mechanisms to improve and sustain pharmacy workforce well-being and resilience
- Deploy pharmacy workforce to support multidisciplinary solutions for improving healthcare workforce well-being and resilience

## Action Collaborative Timeline



## American Society of Health-System Pharmacists

- Vision
  - Medication use will be optimal, safe, and effective for all people all of the time
- Membership Organization
  - Established 1942
  - 45,000 members



## ASHP Vision & Strategic Plan



### Strategic Plan

#### Goal 4: Objectives

- Our Patients and Their Care
  - Goal 4: Improve Patient Care by Enhancing the Well-Being and Resilience of Pharmacists, Student Pharmacists, and Pharmacy Technicians
- Our Members and Partners
- Our People and Performance
- Engage in major national initiatives
- Facilitate the development of education
- Improve the well-being and resilience in postgraduate pharmacy residency training
- Foster research

### ASHP Policy Positions, 1982–2018 2018 Policy Positions

#### 1825

#### CLINICIAN WELL-BEING AND RESILIENCE

Source: Council on Education and Workforce Development

To affirm that burnout adversely affects an individual's well-being and healthcare outcomes; further,

To acknowledge that the healthcare workforce encounters unique stressors throughout their education, training, and careers that contribute to burnout; further,

To declare that healthcare workforce well-being and resilience requires shared responsibility among healthcare team members and between individuals and organizations; further,

To encourage individuals to embrace well-being and resilience as a personal responsibility that should be supported by organizational culture; further,

To encourage the development of programs aimed at prevention, recognition, and treatment of burnout, and to support participation in these programs; further,

To encourage education and research on stress, burnout, and well-being; further,

To collaborate with other professions and stakeholders to identify effective preventive and treatment strategies at an individual, organizational, and system level.

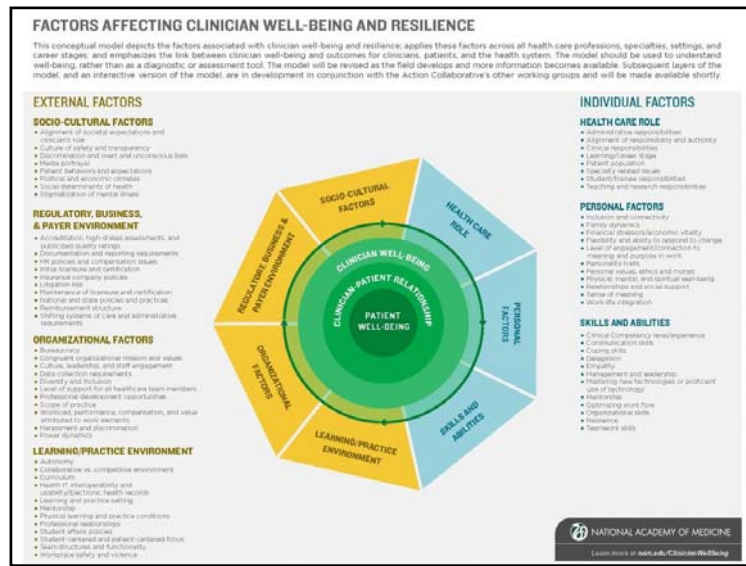
## Collaborative Composition & Commitments

- 36 sponsoring organizations, 100 network organizations:
  - Professional organizations
  - Government
  - Technology and EHR vendors
  - Large health care centers
  - Payors
- 130 commitment statements
  - To provide an opportunity for organizations across the country discuss and share plans of action to reverse clinician burnout and promote clinician well-being.
  - <https://nam.edu/initiatives/clinician-resilience-and-well-being/commitment-statements-clinician-well-being/>

## Creating An All-Encompassing Model

- ✓ Broad enough to define the issue across all healthcare professions
- ✓ Satisfactorily encompasses multiple environments (education, practice)
- ✓ Satisfactorily encompasses multiple stages of development of the health professional
- ✓ Satisfactorily encompasses system and individual issues in ways that are helpful toward developing a solution (e.g. defining without stigmatizing)
- ✓ Lends itself to being a tool for diagnosis, explanation, treatment
- ✓ Serves as a taxonomy for organizing other elements/tools developed as part of this NAM Collaborative

Brigham T, Barden C, Legreid Dopp, A, Hengerer A, et al. A journey to Construct an all-encompassing conceptual model of factors affecting clinician well-being and resilience. National Academy of Medicine, 2018.



## Strategies to Impact Well-Being and Resilience

**ashp**  
pharmacists advancing healthcare®

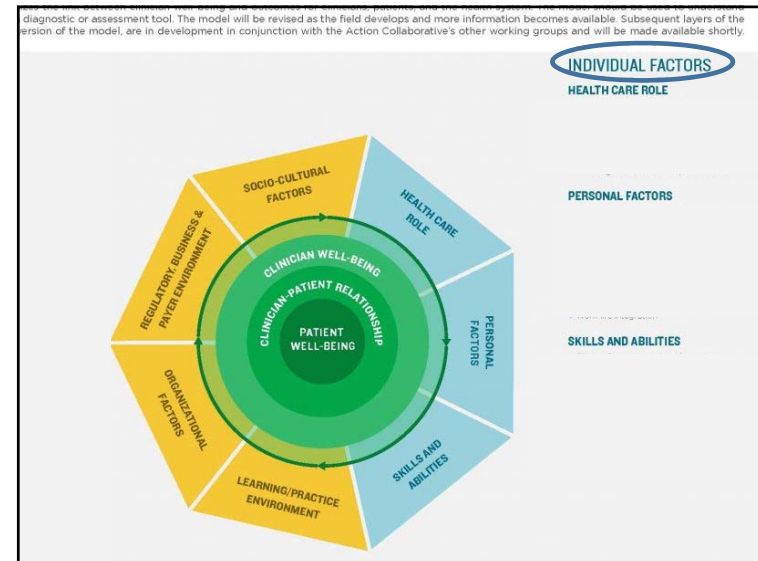
## Clinician Well-being and Resilience

### •Well-being

- The presence of positive emotions and moods.
- The absence of negative emotions.
- Satisfaction with life, fulfillment and positive functioning.
- Physical well-being is also viewed as critical to overall well-being.

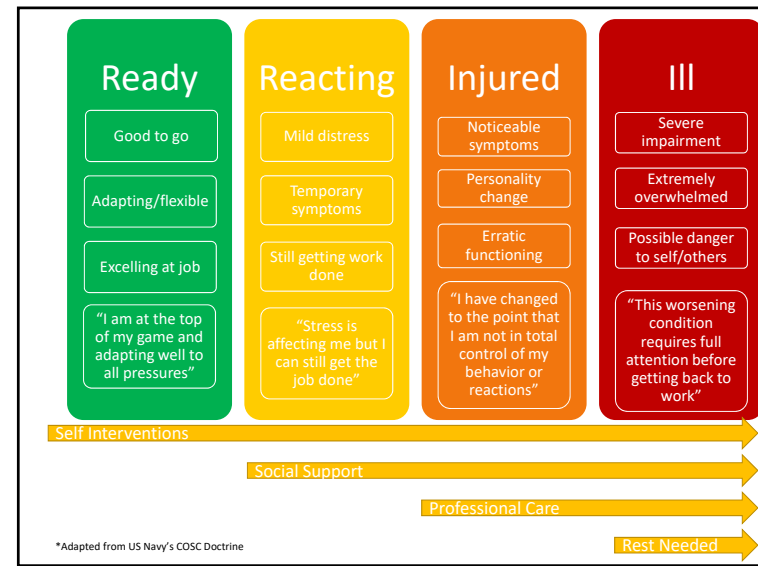
### •Resilience

- Set of individual skills, behaviors, and attitudes that contribute to personal physical, emotional, and social well-being, including the prevention of burnout.



## Resilience & Coping Skills

- Bounce back from adversity, uncertainty, risk or failure, and adapt to changing and stressful life demands
- Hope, optimism, self-efficacy
- Perseverance and passion for long term goals (Grit)



## Mitigating Stress

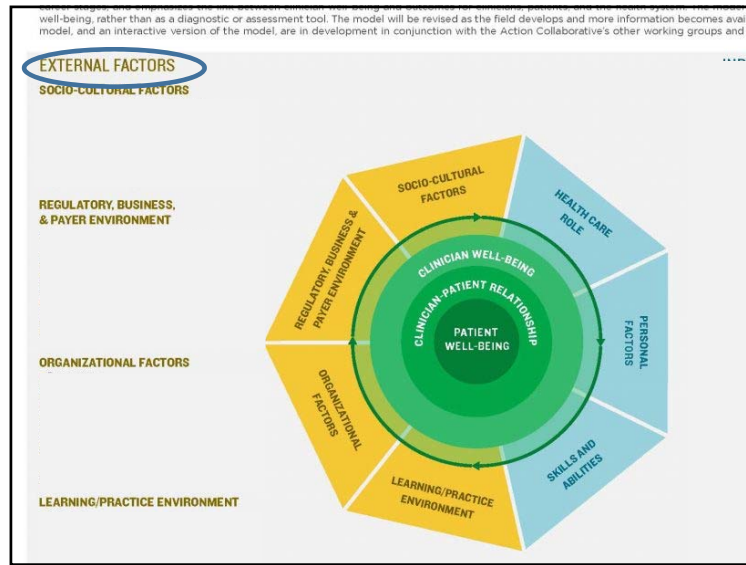
### Self-Care Techniques

- **Monitor** personal stress indicators (sleep, eating, agitation, etc)
- **Decompress** with healthy transitions (teatime, yoga, journal, breathwork, music)
- **Record** three good experiences from the day, savor those positive moments and plan for good experiences tomorrow
- **Speak** with trusted people, maintain social connections

### Resiliency Competencies

- Awareness
  - Noticing the right information
    - Sensations, thoughts, environments
- Regulation
  - Of self and others' stress reactions and emotions
- Leadership
  - Toward meaningful personal and team actions

What is one strategy that you (individual) are going to employ to support well-being and resilience?



## Strategies to Alleviate Burnout in Healthcare Professionals

Risk Factors Associated With Burnout  
*Am J Health-Syst Pharm. 2017; 74:e576-81*

Risk Factor	Strategy to Alleviate Risk
Workload	Permitting time at the workplace to recover from a stressful event
Control	Clearly defined roles and expectations from organizational leadership
Reward	Identify suitable rewards to recognize achievements, provide opportunities to teach or mentor trainees
Community	Promote participation in professional organizations
Fairness	Transparency in decision-making
Values	Align personal expectations with organizational goals
Job-person incongruity	Evaluate and align job responsibilities with personal and professional expectations

### Executive Leadership Strategies

- Acknowledge & assess the issue
- Identify impediments
- Harness the power of leadership
- Implement system approaches
- Cultivate community
- Use rewards & incentives wisely
- Align values & strengthen culture
- Promote flexibility and work-life integration
- Provide resources to promote self-care
- Use improvement science to test



1. Shanafelt TD, Noseworthy JH. Executive leadership and physician well-being: Nine Organizational Strategies to promote engagement and reduce burnout. Mayo Clin Proc. 2017;92(1):129-146. 2. Perlo J, Balik B, Swensen S, Kabcenell A, Landsman J, Feeley D. JHI Framework for Improving Joy in Work. JHI White Paper. Cambridge, Massachusetts: Institute for Healthcare Improvement; 2017.

What is one strategy you think your supervisor/institution can employ to support well-being and resilience?

Looking ahead

### Educate Yourself on Burnout

- Webinars
  - [Extinguishing the Burnout: Yourself and Your Team](#)
  - [Tame the Flames of Burnout: Tools for Building Resilience in Your Workforce](#)
  - [Leadership Burnout and Strategies for Burnout Prevention](#)
- More Resilience sessions planned for:
  - 2018 National Pharmacy Preceptors Conference
    - Creating a Culture of Resident Well-Being
    - Building Resilience in Residency Training It Takes a Village
    - Fueling Your Fire Identifying and Managing Preceptor Burnout
  - 2018 Conference for Pharmacy Leaders
    - Workforce Resilience Developing an Open and Successful Environment
  - 2018 Midyear Clinical Meeting







Questions?  
Ideas?  
Considerations?



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## New Compounding Regulations

(or how I spent my summer vacation)

Janet Hinkes, PharmD, MBA  
Clinical Staff Pharmacist & IV Room Coordinator  
UI Health

## New Compounding Regulations

The author has no actual or potential conflict of interest in relation to this activity

Janet Hinkes, PharmD, MBA  
Clinical Staff Pharmacist & IV Room Coordinator  
UI Health

## *Learning Objectives for Pharmacists & Technicians*

- Describe three sources of contaminants to compounded sterile preparations.
- Identify organizations that have enforcement authority with respect to USP <797>.
- List three proposed changes to USP <797>: Separation of Hazardous Drug standards, new product categories, new beyond use date.
- Identify important remaining dates in the USP <797> timeline to enforcement

## What is USP?

The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that **sets standards** for the

- identity,
- strength,
- quality, and
- purity of

**medicines**, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide.

## United States Pharmacopeia (USP)

- Chapters **below** <1000>
  - Compliance is **mandatory**
- Chapters above <1000>
  - Informational and advisory
- **USP <797>** Pharmaceutical Compounding – Sterile Preparations
  - First released in 2004
  - revision in 2008
  - [another revision pending](#)
  - anticipated to become [official December 1, 2019](#)

## USP <797> Pharmaceutical Compounding—Sterile Preparations Chapter Objective

Chapter <797> should be followed to **minimize harm**, including death, to patients in the use of Compounded Sterile Preparations (CSP) due to:

- Microbial contamination (nonsterility)
- Excessive bacterial endotoxins
- Variability from intended strength of correct ingredients
- Physical and chemical incompatibilities
- Chemical and physical contaminants
- Ingredients of inappropriate quality

## Quick Quiz

Test your memory from elementary school

What is a NOUN?

- word that provides a description
- an action word
- a word that names a person, place or thing

## USP <797> Pharmaceutical Compounding—Sterile Preparations Factors affecting risk of contaminants

Factors affecting risk are NOUNs

- Persons
- Places
- Things

USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk of contaminants

- Persons
  - Personnel must be trained and properly garbed
- Places
  - Facilities must be designed appropriately
  - Equipment must be selected and maintained
- Things
  - Components must be sterile
  - Gowning & gloving with appropriate materials



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk of contaminants - Personnel

Personnel must be trained

- Aseptic technique
- Hand hygiene and garbing
- Cleaning and disinfection
- Use of equipment
- Documentation



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk of contaminants - Personnel

Personnel must be tested

- Written testing to include
  - Methods of preparation
  - Calculations
  - Policies on hand hygiene and garbing
  - Policies on cleaning and disinfection
- Every 12 months



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk of contaminants - Personnel

Personnel must be tested

- Hands-on demonstration of skills
    - Hand hygiene and garbing
    - Media fill
    - Glove sampling
  - Every 6 months for **all** compounding personnel
- \*\*\* this is a change \*\*\*  
formerly only annually unless preparing high risk CSPs



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## Quick Quiz

### Factors affecting risk - Personnel

Hand hygiene & garbing observation as well as media fill & glove sampling must occur

- A. Every month
- B. Every 3 months
- C. Every 6 months
- D. Every 12 months



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk – facilities & equipment

- Places
  - Facilities must be designed appropriately
  - Equipment must be selected and maintained



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk – Facilities & equipment

### Facility design - Cleanroom suite

- Anteroom
  - ISO class 8 or better
- Buffer area
  - ISO class 7 or better
- Primary engineering control
  - ISO class 5 or better
- Provides clean environment for compounding



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk – Facilities & equipment

### Equipment selection

- Primary engineering control
  - ISO class 5 or better
  - Biological safety cabinet
  - Laminar airflow workbench – horizontal or vertical
  - Integrated vertical laminar airflow zone
  - Restricted access barrier system = isolator



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk – Facilities & equipment

- \*\*\* no change under revised USP <797> for
- Facility design
- Equipment selection for primary engineering control



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk - components

Components must be sterile

- Include only sterile components or
- Include nonsterile components and undergo sterilization
  - Filtration
  - Terminal sterilization: steam, dry heat, radiation



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USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk - garb

Gowning & gloving with appropriate materials

- Low shedding materials
- Fit to prevent skin exposure
  - People shed 1 million skin cells each day
- Sterile gloves
  - Sterile isopropyl alcohol



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
Factors affecting risk – components and garb

- \*\*\* no change under revised USP <797> for
- Gowning and garb selection of materials
- Component sterility



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### Quick Quiz

Risk of contaminants when compounding

Name 3 risk factors that impact compounded sterile preparations (CSP)

- A. Distribution methods, personnel, equipment
- B. Personnel, facilities, labeling
- C. Personnel, equipment, facility



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

### PRE Quiz

Enforcement of USP standards

Enforcement of USP standards is carried out by

- A. FDA and DEA
- B. USP during surprise visits
- C. FDA and TJC as well as other organizations
- D. There is no enforcement organization



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

### Who enforces USP Standards?

USP's drug standards are enforceable in the United States by

- The Food and Drug Administration (FDA)
- State regulators – Boards of Pharmacy
  - Illinois Board of Pharmacy
- The Joint Commission (TJC)
- Center for Medicare and Medicaid Services (CMS)



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

### Who enforces USP Standards?

USP's drug standards are enforceable in the United States by

- The Food and Drug Administration (FDA)
  - outsourcing facilities under section 503B are primarily overseen by FDA
  - inspected by FDA according to a risk-based schedule
- State boards of pharmacy
  - Not all states explicitly require compliance with USP
  - Illinois does **NOT** reference USP <797> in the Pharmacy Practice Act, Section 1330.670 Compounded Sterile Preparation Standards



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

## Who enforces USP Standards?

USP's drug standards are enforceable in the United States by

- The Joint Commission (TJC) assesses sterile compounding activities during surveys
  - Expect increased attention on sterile compounding
  - Noted in TJC newsletter October 2017
- Center for Medicare and Medicaid Services (CMS)
  - pharmaceutical services Condition of Participation (CoP)
  - current accepted standards of practice including United States Pharmacopeia (USP) standards



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

## Quick Quiz

Enforcement of USP standards

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- A. FDA and DEA
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USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

- Hazardous drug standards removed
  - see USP <800>
- Risk levels renamed to CSP categories
  - low, medium, high revised to
  - Category 1 and Category 2
- New beyond use dating (BUD)
- Increased personnel testing
  - previously noted



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

Risk levels renamed to CSP categories

- low, medium, high revised to
- Category 1
  - Does not require classified area for PEC
  - Shorter BUD than category 2
- Category 2
  - Must be prepared in classified room
  - BUD can vary



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING



## Quick Quiz

### Changes to USP <797>

USP <797> changes that impact hospital compounding of sterile preparations include

- A. Risk levels A through E with shorter BUD
- B. Additional sections on hazardous drug compounding
- C. Hazardous drugs segregated in <800> and only 2 CSP categories



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

### Category 1

- Does not require classified area for PEC
- Segregated compounding area
- Shorter BUD than category 2
  - Room temp 12 hours
  - Refrigerated 24 hours



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

### Category 2

- PEC must be in a class 7 buffer area
- Anteroom must be class 8 or better
- Longer BUDs than category 1
- BUD based on
  - Starting components
  - Sterility tests if applicable
  - Storage conditions



ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS, 2018 ANNUAL MEETING

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

### Category 2 BUD based on

- Starting components
  - 100% sterile vs. some non-sterile
- Terminal sterilization, if performed
- Sterility tests, if performed and passed
- Storage conditions
  - Room temperature, refrigerated, frozen



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Table 12. BUDs for Category 2 CSPs

Preparation Characteristics		Storage Conditions		
Sterilization Method	Sterility Testing Performed and Passed	Controlled Room Temp	Refrigerator	Freezer
Aseptically prepared CSPs	No	One or more nonsterile starting components 1 days	One or more nonsterile starting components 4 days	One or more nonsterile starting components 45 days
		Only sterile starting components 4 days	Only sterile starting components 9 days	Only sterile starting components 45 days
	Yes	30 days	45 days	60 days
Terminally Sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New

Table 12. BUDs for Category 2 CSPs

- Terminal sterilization with sterility testing provides the longest BUDs
- Room temperature BUDs are extended

Table 12. BUDs for Category 2 CSPs

Preparation Characteristics		Storage Conditions		
Sterilization Method	Sterility Testing Performed and Passed	Controlled Room Temp	Refrigerator	Freezer
<b>Aseptically prepared CSPs</b>	<b>No</b>	One or more nonsterile starting components 1 days	One or more nonsterile starting components 4 days	One or more nonsterile starting components 45 days
		<b>Only sterile starting components 4 days</b>	<b>Only sterile starting components 9 days</b>	<b>Only sterile starting components 45 days</b>
	Yes	30 days	45 days	60 days
Terminally Sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

USP <797> Pharmaceutical Compounding—Sterile Preparations  
What's New - BUDs for Category 2 CSPs

#### COMMON hospital compounding:

- Sterile components with aseptic technique
  - Common doses of antibiotics from bulk vials
  - ex: Vancomycin, cefazolin
- No terminal sterilization and no sterility testing
- Room temperature 4 days \*\*\* change \*\*\*
- Refrigerator 9 days
- Freezer 45 days

### USP <797> Pharmaceutical Compounding—Sterile Preparations What's New - Recap

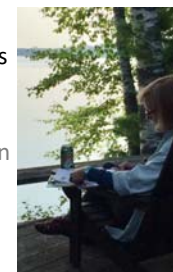
- Hazardous drug compounding and handling moved to <800>
- Risk levels replaced by **CSP categories**
  - Category 1 – segregated compounding area
  - Category 2 – prepared in IV suite
- BUD depends on components and storage temperature
  - Category 1 – short BUD
  - Category 2 – some extended BUD
    - 4 days room temp for commonly prepared CSPs
    - All components are sterile, Aseptic technique, No sterility testing



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### Timeline for ICHP Annual Meeting presenters

- **July 26, 2018 – submit** learning objectives and methods to ICHP
  - July 27, 2018 – proposed <797> Pre-Posted on USP website
- August 9-13, 2018 – Janet on vacation in the Northwoods
- **August 16, 2018 – submit** final slides to ICHP
  - September 4, 2018 - <797> to be formally published in Pharmacopeial Forum
  - September 5, 2018 – Open Microphone Session
- September 13-15, 2018 – ICHP Annual Meeting



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### Timeline for USP <797> update

- July 27, 2018 – proposed <797> Pre-Posted on USP website
- September 4, 2018 - <797> to be formally published in Pharmacopeial Forum
- September 5, 2018 – Open Microphone Session
- November 30, 2018 – Public Comment Period for <797> will close
- **June 1, 2019** – Intended date of publication of <797> in *USP-NF*
- **December 1, 2019** – Anticipated Official Date for <797>



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### Quick Quiz Dates to watch for USP <797>

USP <797> is expected to become official on

- January 1, 2019
- June 1, 2019
- December 1, 2019
- As soon as this presentation ends 🤖



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## Changes to Pharmacy Practice

When USP <797> becomes official on December 1, 2019\*

- More frequent testing of personnel
  - Every 6 months for media fill and glove sampling
- Longer BUD for some compounded sterile preparations (CSP)
  - 4 days at room temperature for Category 2 CSPs
    - All sterile additives
    - Class 5 PEC within Class 7 buffer area (cleanroom suite)
    - Aseptic technique – no sterility testing



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## <797> Version is still not final\*

- Questions remain about the final version of USP <797>
- Open for comments until November 30, 2018

Any questions?



jhinke3@uic.edu



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## Reference sources

- US Pharmacopeial Convention General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. Download the Proposed Revision to GC <797>. Available at <http://www.usp.org/compounding/general-chapter-797>. Accessed August 6, 2018.
- Reducing Risk Associated with Sterile Medication Compounding. The Joint Commission Perspectives, the Official Newsletter of the Joint Commission. October 2017; Vol 37; Number 10: 12-13.



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# PROS & CONS OF RFID TECHNOLOGY

By Cristina Aguilar  
Pharmacy Technician Specialist  
Northwestern Memorial Hospital

The speaker has no conflict of interest to disclose.

## Learning Objectives — Pharmacists and Technicians

1. Explain the benefits and challenges of using RFID technology when filling OR trays
2. List other areas within the pharmacy that can benefit from RFID technology

## Session overview

- What is RFID Technology?
- RFID in real time
- RFID to reduce labor costs
- RFID for inventory management
- RFID to reduce human error

## WHAT IS RFID TECHNOLOGY?

\* RFID abbreviated for: **R**adio **F**requency **I**dentification



\* Purpose: to help identify a person, object or animal that has been tagged with a smart label.

### 3 Components for RFID Technology

- \* Smart Label: Stores all the information
- \* Antenna: Helps communicate
- \* RFID Reader (interrogator): helps transmit information to a computer system

## RFID in Real Time

(track and tracing)

*Pros -*

**Time efficiency:** Cuts down time when filling or verifying a tray or a kit.

**Real time data:** Gives the benefit of providing data about recalls, drug usage, expires, etc in real time.

*Cons-*

**Time consuming:** If a new medication has not been previously used or added to the inventory, it has to be added manually in order for the drug or item to be identified.



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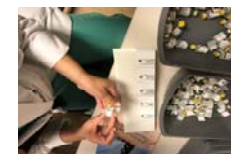
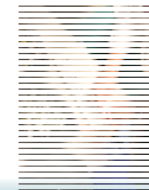
## RFID to Reduce Labor Costs

*Pros-*

A process that required multiple people can now be completed can now be done within a matter of minutes

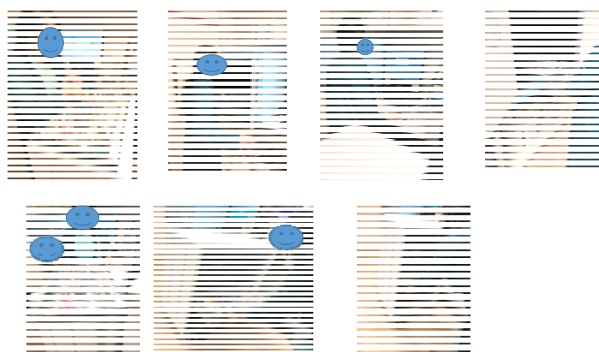
Example: A pharmacist can be freed for other clinical needs

*Cons-* it takes people to tag the item or purchase more expensive pre-tagged medication.



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## RFID to Reduce Labor Costs



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## RFID for Inventory Management

Exact data in the smart label

*Pros -*

Reduces the amount of waste and helps identify the problem; helps to the contribution of identifying par levels, fast movers, expired reports, etc.

*Cons-*

\*Labels are expensive

\*Interference problems

\*No way to track damaged labels



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## RFID to Reduce Human Error

### Pros-

Missing and expired meds will be identified when processing an OR tray or kit.

Ex./ Even if an item is missed during filling process the reader will pick up the missing or expired medications

### Cons-

Damaged label will not read.

Used items will still scan



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## What are the benefits of up to date data?

- A. Provides real time data
- B. No benefits
- C. I do not remember

## What is a CON to reducing labor costs?

- A. Purchase higher cost pre-tagged medications
- B. Pharmacist gets to focus on other clinical needs

## What are three components of RFID technology?

- A. Smart label, antenna, RFID reader
- B. Ondansetron, label, antenna
- C. Drug, computer software, label



### Bibliography

Coustasse, Alberto, et al. "Impact of Radio Frequency Identification Technologies on the Hospital Supply Chain." *Perspectives in Health Information Management*, 1 Oct. 2013.

Zhu, Xiaowei, et al. "A Review of RFID Technology and Its Managerial Applications in Different Industries." *Journal of Engineering and Technology Management*, vol. 29, no. 1, 2012, pp. 152–167., doi:10.1016/j.jengtecman.2011.09.011.

Vecchione, Anthony. "Patient Safety Driving Increased RFID Use in Hospitals." *Healthcare IT News*, 30 June 2015, [www.healthcareitnews.com/news/patient-safety-driving-increased-rfid-use-hospitals](http://www.healthcareitnews.com/news/patient-safety-driving-increased-rfid-use-hospitals).



## Leadership Gems

Brittany Huff, PharmD  
Clara Gary, CPhT



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## Advancing Pharmacy Technician Roles

Brittany Huff, PharmD

Contributions made by Desi Kotis, PharmD, FASHP

The speaker and contributor have no conflicts of interest to disclose.



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## Learning Objectives – Pharmacist and Technician

- Explain why advanced pharmacy technician roles are needed in the pharmacy
- Describe the training involved with advanced pharmacy technician roles



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## Expanding Roles of Pharmacy Technicians

Pharmacist and pharmacy technicians are considered to be one of the most accessible healthcare providers

Pharmacy technicians play an increasingly important role in public safety

As pharmacies expand patient care services, the role of and need for pharmacy technicians also continue to expand



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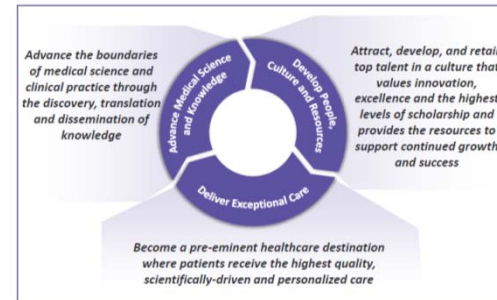
## Pharmacy Practice Initiative Model

- Supports more extensive use of pharmacy technicians to free pharmacists from drug distribution activities.
- Advancement of technicians
  - Assist with the dispensing responsibilities of pharmacists.
  - Assist in the facilitation of these services.



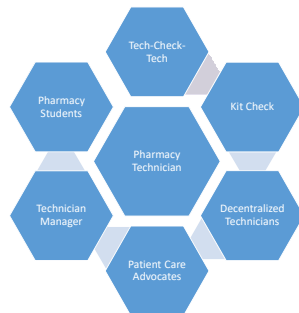
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## Three High Level Goals



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## Advancements in Pharmacy Technicians



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## Tech-Check-Tech

- Specialized Technician
  - Technician autonomy
  - Expanded role
- Frees up pharmacist to focus on patient care
- Safety and Quality Assurance measures in place



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## RFID Technology

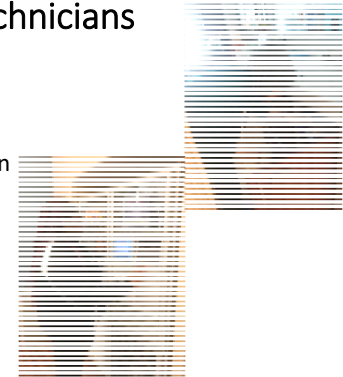
- Technicians have COMPLETE ownership
- System designed to accurately check trays
  - Anesthesia trays
  - Emergency crash cart trays
- Uses RFID technology to ensure accuracy of medication



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## Decentralized Technicians

- Technician ownership of entire floor
- Faster medication delivery
- Improved nursing and patient satisfaction



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## Patient Care Advocates Specialty Pharmacy Technicians

- Script data entry
- Benefits investigation
- Prior authorizations
- Financial assistance
  - Copay cards
  - Enrollment in manufacturer assistance programs
  - Finding funding using grants and other foundation programs
- Facilitating shipment of the drug
- Call center services
  - Refill management
  - Facilitate answering questions



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## What are examples of ways we can appropriately expand technician roles?

- Discharge Pharmacy Technician
- Pharmacy Analyst Technician
- Informatics Technician
- Medication Reconciliation Technician
- All of the Above



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## What are examples of advanced pharmacy technician roles at your institution?



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## Optimizing Utilization of Pharmacy Technicians

- Many transitions have occurred to meet the needs of patients and society.
- Increased need for clinical services and dispensing.
  - Time becomes a limiting factor in the ability of the pharmacist to provide quality patient care.
- Free pharmacists from nonclinical tasks and spend more time devoted to patient care.
- How do we appropriately define what is better utilization of pharmacy technician?



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## Optimizing Utilization of Pharmacy Technicians

- Goal: enhance the profession of pharmacy, improve medication use, and advance patient care.
- Expand the technician to reduce pharmacist workload.
- Expansion should not conflict with the role of the pharmacist
  - Avoid the application of clinical knowledge, drug use review, or recommendations in therapy.



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## Advancing the Role of the Pharmacy Technician: A Systematic Review

- Objective: Summarize literature on advancing pharmacy technicians roles, including types of training and potential costs and benefits to the technician and pharmacy.

Top three training mechanisms	
Informal on the job training led by pharmacists or other technicians	58%
Formal technician training programs by and apart from the employer	61%
Test based certification to demonstrate competency after training	36%



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## Advancing the Role of the Pharmacy Technician: A Systematic Review

### Direct and Indirect Costs

- i. Time for both the technician and the educator
- ii. Supplies in the training
- iii. Cost to cover routine operations in the pharmacy during the training when appropriate

### Indirect Benefits to the Organization

- i. Cost savings through potential elimination of pharmacist positions
- ii. Increase in potential revenue through expanded clinical services
- iii. Increased efficiency
- iv. Better patient adherence
- v. More satisfaction from other departments and patients in pharmacy services



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## Advancing the Role of the Pharmacy Technician: A Systematic Review

### Direct and Indirect Benefits to the Pharmacist and Technician

- i. Increases in technician wages
- ii. More job satisfaction for both technicians and pharmacists
- iii. Stronger career ladder for technicians
- iv. More desirable work schedule for the technician
- v. Improved confidence of the technician in their knowledge and ability to perform particular skills



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## Training

- Train all of its registered pharmacy technicians in the following topics as they relate to the practice site:
  1. The duties and responsibilities of the technicians and pharmacists.
  2. Tasks and technical skills, policies, and procedures.
  3. Compounding, packaging, labeling, and storage.
  4. Pharmaceutical and medical terminology.
  5. Record keeping requirements.
  6. The ability to perform and apply arithmetic calculations.



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## Role in Counseling

- A pharmacy technician may participate the following aspects of patient counseling under the supervision of a pharmacist:
  - (1) Obtaining medication history;
  - (2) Providing the offer for counseling by a pharmacist or student pharmacist.
  - (3) Acquiring a patient's allergies and health conditions.



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## Continuing Education

- As a condition for the renewal of a license as a registered certified pharmacy technician, the licensee shall provide evidence of ACPE approved CE credit hours:
  - Total of 20 hours during the 24 months preceding the expiration date of the certificate
  - One hour must be in the subject of pharmacy law
  - One hour must be in the subject of patient safety



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## Pharmacy Technician Stakeholder Consensus Conference

- Sponsored by the Pharmacy Technician Certification Board
- Collaboration with the Accreditation Council for Pharmacy Education and the American Society of Health-System Pharmacists
- Conference Focus:
  - Provide recommendations regarding the definition, education, entry-level requirements, advance practice, certification, and regulation of pharmacy technicians
- Conferees were polled on their level of agreement or disagreement regarding 59 statements associated with unresolved pharmacy technician issues



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## Pharmacy Technician Stakeholder Consensus Conference

Issue	Results of Conference Polling
Advance pharmacy technician practice	Conferees generally agreed that the profession of pharmacy's immediate priority, with respect to technician issues, should be development of standards related to entry-level education and that advanced roles for technicians (and related education and credentials) will evolve over time



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## Limitations

National requirements for pharmacy technician certification

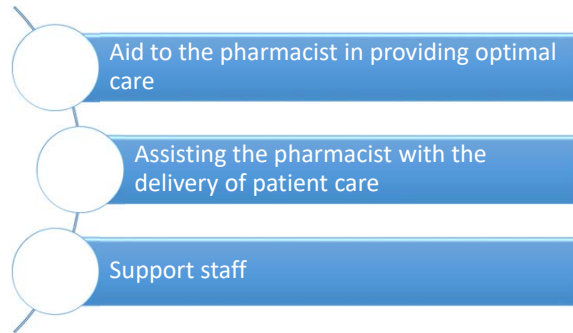
Standards for pharmacy technician education

Clearly defined legal roles for the title of pharmacy technicians



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## Who Benefits?



A systematic review analyzing advancement of pharmacy technicians identified the most common training methods being all of the following except:

- A. Informal on the job training led my pharmacists or other technicians
- B. Formal technician training programs by and apart from the employer
- C. Test based certification to demonstrate competency after training
- D. All of the above were identified as training methods

## Expanding Pharmacy Technician Roles

- As pharmacy practice continues to advance, one must remember to consider the role of the pharmacy technician and their significant contributions to the profession.
- Adopt a common vision for pharmacists and pharmacy technicians qualifications
  - Accreditation-education-examination-licensure model
- Licensed pharmacy technicians with standard core knowledge
  - Provide the pharmacist with a uniformly educated and competent pharmacy technician

## Expanding Pharmacy Technician Roles

By elevating pharmacy technician education and roles, pharmacists are able to rely more confidently on their technician's work, allowing more time for clinical work and patient care



## References

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## Advancing Pharmacy Technician Roles

Brittany Huff, PharmD

The Speaker Has Nothing to Disclose



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# ICHP 2018 ANNUAL MEETING

LEADERSHIP GEMS  
PHARMACY RX TECHS CARES  
September 14th 2018

**Speaker: Clara Gary**

The speaker has no conflicts of interest to disclose.



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## Learning Objectives

- Recognize that Pharmacy Technicians are paraprofessionals
- Explain what "RX" Tech CARES means



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## Do I look Surprised?



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## MY CAREER- NORTHWESTERN MEMORIAL TO MICHAEL REESE



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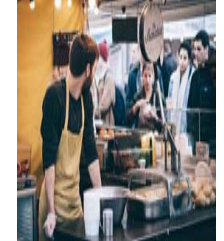
## MY CAREER AT UNIVERSITY OF ILLINOIS MEDICAL CENTER-UI HEALTH



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## How do you see yourself?



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## What is a paraprofessional?

*Paraprofessional is a person trained to assist a doctor, lawyer, teacher, or other professional, but not licensed to practice in the profession.*

*[www.dictionary.com](http://www.dictionary.com)*

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## We are Paraprofessionals!



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## *Pharmacy Technicians are...*

Health paraprofessionals that provide a mixture of services in settings such as hospitals, health clinics, schools, pharmacies, physician offices, and nursing care facilities. Health paraprofessionals are trained to work directly with patients, serving an important role assisting providers of care and collaborating with the healthcare clinicians for improved patient outcomes.

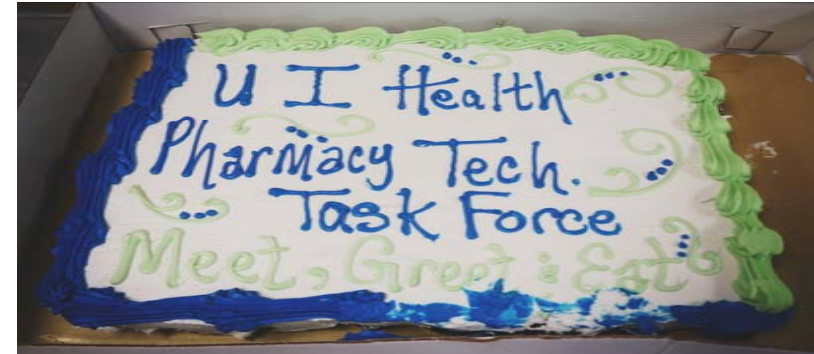
## What we do:

- Greet patients and intake scripts confirming 2 patient identifiers
- Perform data entry
- Complete benefit investigation
- Initiate prior authorizations
- Fill prescriptions and monitor inventory
- Compound products
- Cash out medication and OTCs
- Deliver medication to the patient, nurse or clinician
- We free up Pharmacist to concentrate of dispensing, counseling and other clinical activities

## Which group are paraprofessionals?

- A.) Fast food employees
- B.) Lawyers
- C.) Pharmacy Technicians
- D.) Migrant Workers
- E.) Baristas

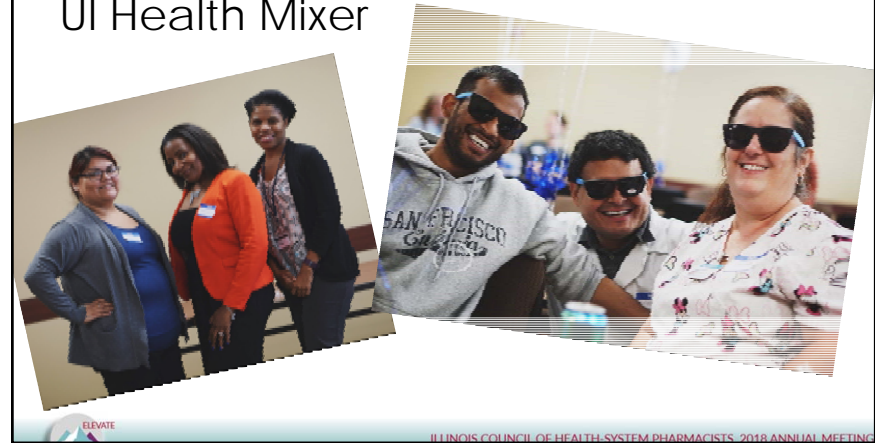
## UI Health Mixer



## UI Health Mixer



## UI Health Mixer



## How RX Techs CARES!!

- How to prepare yourself for advancement
- Contribute- Seek more responsibility
- Accountable- Learn from your mistakes
- Respectful- Listen with compassion and empathy and respond properly
- Excel- Go above and beyond expectations
- Serve- Find a professional organization and share your talents and time

## How did these technicians achieve success?

- They built trust with their pharmacists!
- They found an area that they were interested in or could be passionate about!





## How did these technicians achieve success?

- They worked on improving their skills to earn advancement!
- They recognized opportunities and stepped up!



## To be successful as a Pharmacy Technician, you must possess...

- Integrity and reliability
- Excellent customer service skills
- Ability to listen and follow directions
- Attention to detail
- Responsibility and compassion
- Ability to multi-task and be organized
- Exceptional communications skills
- Understanding of basic math

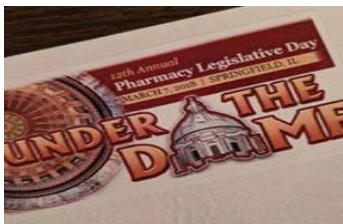
## What does RX CARES Stand for?

- A.) Compassionate, Accountable, Respectful, Excel, Serve
- B.) Contribute, Accountable, Respectful, Experienced, Serve
- C.) Communicate, Achievement, Recognized, Exceptional, Skilled
- D.) Contribute, Accountable, Respectful, Excel, Serve
- E.) Crabby, Argumentative, Rabble-rouser, Egomaniac, Self-serving

## Get Involved!



## Legislative Day 2018



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## Our UI Health Pharmacy Family!!



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## Find a Pharmacist Mentor!!



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## Welcome our new ICHP Technician Representative!!!



**ICHP**  
Leadership  
Profile

Kristine VanKuiken,  
Pharmacy Technician Specialist  
[keepposted.ichpnet.org](http://keepposted.ichpnet.org)

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## ISMP Best Practices for 2018-2019

Ann Jankiewicz, PharmD, BCPS, FASHP  
Medication Safety Officer  
Rush University Medical Center  
Chicago, IL

The speaker has no conflicts of interest to disclose.



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Are you familiar with the Institute for Safe Medication Practice (ISMP) Best Practices?

- A. YES
- B. NO



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Have you worked on implementing an ISMP Best Practice?

- A. YES
- B. NO



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### Learning Objectives – Pharmacists and Technicians

- List the Institute for Safe Medication Practices (ISMP) 2018-2019 Targeted Medication Safety Best Practices.
- Review strategies for compliance with the ISMP recommendations.
- Identify barriers to achieving compliance with the ISMP recommendations.



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*“The purpose of the Targeted Medication Safety Best Practices for Hospitals is to **identify, inspire, and mobilize widespread, national adoption of consensus-based best practices for specific medication safety issues** that continue to cause fatal and harmful errors in patients, despite repeated warnings in ISMP publications.”<sup>1</sup>*

<sup>1</sup><http://www.ismp.org/Tools/BestPractices/TMSBP-for-Hospitalsv2.pdf>

## History of the ISMP Best Practices

- ISMP Best Practices 2014-2015
  - 6 best practices
- ISMP Best Practices 2016-2017
  - #2 and #3 revised
  - #7-11 added
- ISMP Best Practices 2018-2019
  - #4 and #7 revised
  - #12-14 added
- Full compliance ranges from 38% to 94%

## Best Practice #1: Dispense vincristine and other vinca alkaloids in a minibag (not syringe)

- To avoid the mistake of administering vincristine intrathecally (can be fatal)
- RUMC changed to minibags only for adults and peds in inpatient and outpatient pharmacies in 2014
- National Comprehensive Cancer Network (NCCN) started their “Just Bag It!” campaign for safe vincristine handling in 2016
- The Oncology Nursing Society (ONS) also endorsed this change in 2016 and has recommendations for safe administration
- At RUMC, we do the following
  - Gravity drip when given peripherally
  - Nurses to remain with the patient to monitor for extravasation
  - Flush line after infusion completed

## BEST PRACTICE 2: METHOTREXATE

a) Use a weekly dosage regimen default for oral methotrexate in electronic systems when medication orders are entered.

Dose:  mg

Route:

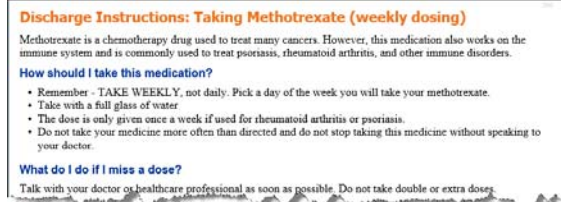
Frequency:

b) Require a hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders.

## BEST PRACTICE 2: METHOTREXATE

c) Provide specific patient and/or family education for all oral methotrexate discharge orders.

- Developed one page patient discharge education sheet specific to weekly oral methotrexate



- To do—Add teaching point to Patient Education Activity so that teaching can begin during hospital stay
  - Include reminder to give patient/family discharge education sheet

## BEST PRACTICE 3:

- a) Weigh each patient as soon as possible on admission and during each appropriate outpatient or emergency department encounter. Avoid the use of a stated, estimated, or historical weight.
- b) Measure and document patient weights in metric units only (kg).

**Stated Weight Date 5/9/18**

Department	Count
EMERGENCY DEPARTMENT (TOWER)	18
T11W- SURGICAL	18
A05- OPERATING ROOM	13
K11- ADULT PSYCH	9
A05- PREP / PHASE II	7
A75- MEDICAL / SURGICAL	6
T14W- MEDICAL / ONCOLOGY	6
T02- OPERATING ROOM	5
A7N- MEDICAL	4
B0N- MEDICAL	4
B0N- MEDICAL OBSERVATION	3
T04- INTERVENTIONAL SUITS	3
T05- OPERATING ROOM	3
T05- PREP / PHASE II	3
A05- MEDICAL	2
T02- PREP / PHASE II	2
T10E- NICU	2
T11E- NICU	2
T11E- NICU / SURGICAL	2
T12W- NEUROSC SERVICES	2
A06- MOTHER-BABY UNIT	1
B0N- NICU	1
T04- PREP / PHASE II	1
T06W- LABOR DELIVERY	1
<b>Total</b>	<b>116 patients</b>

**Weighting Patients**

NSOP-0178

Nursing

Nursing Standards of Practice - General

1. Patients are weighed on the appropriate scale based on their physical condition.
2. Daily weight monitoring is enhanced if performed at the same time of day, on the same scale, and with the same liner or clothing.
3. It is preferable to weigh the patient before breakfast.

1. All patients upon admission will have a weight recorded.

- Admission weight is recorded in Epic as dosing weight unless otherwise ordered by the physician/Advanced Practice Provider (APP).

**NSOP Best Practice #3**

1. Weigh each patient as soon as possible on admission and during each appropriate outpatient or emergency department encounter. **Avoid the use of a stated, estimated, or historical weight.**

2. Measure and document patient weights in metric units only.

## BEST PRACTICE 3: Weighing Patients

- Barriers to implementing Best Practice #3
  - Leadership buy-in
    - Inpatient and outpatient
    - Also buy-in from all disciplines (MD, RN, Engineering)
  - Cost
    - Buying new scales
    - Buying new carts with scales for the ED
  - Technology
    - Not able to lock down only entering weights in metric units
    - Not able to lock down all current bed scales and standing scales to metric only
  - Size of the organization
    - # of scales, bed scales needed
    - Many clinics with scales
  - We think in "pounds"

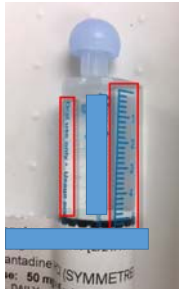
**BEST PRACTICE 4: (REVISED)** Ensure that all oral liquid medications that are not commercially available in unit dose packaging are dispensed by the pharmacy in an oral or ENFit syringe.

- RUMC--Oral liquids are dispensed by pharmacy in oral syringes marked with Oral Use Only
- Conversion to ENFit is in discussion stage
- Do not stock bulk oral solutions of medications on patient care units



**BEST PRACTICE 5:** Purchase oral liquid dosing devices (oral syringes/cups/droppers) that only display the metric scale.

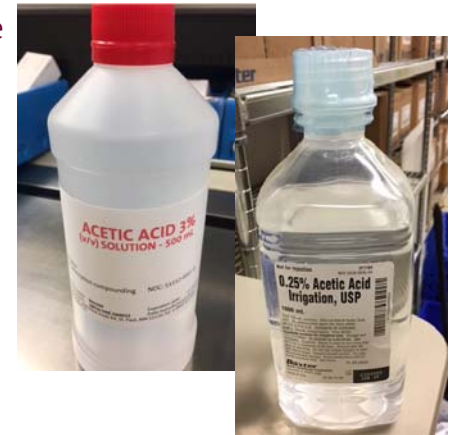
- All medicine cups changed on nursing units and inpatient pharmacy October 2015
- All oral syringes have metric scale markings only



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**BEST PRACTICE 6:** Eliminate glacial acetic acid from all areas of the hospital.

- Removed from RUMC inpatient pharmacy in 2013
- Purchase dilute acetic acid products



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How does your institution keep neuromuscular blockers (rocuronium, cisatracurium, vecuronium) away from other medications?

**BEST PRACTICE 7: (REVISED)** Segregate, sequester, and differentiate all neuromuscular blocking agents (NMBs) from other medications, wherever they are stored in the organization.



WARNING: PARALYZING AGENT—  
Causes Respiratory Arrest  
PATIENT MUST BE VENTILATED

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**BEST PRACTICE 10:** Eliminate all 1,000 mL bags of sterile water (labeled for “injection,” “irrigation,” or “inhalation”) from all areas outside of the pharmacy.

- Respiratory Therapy stocked 1L Sterile Water for Inhalation
  - Request to change to 2L bag
    - Concern if 2L bag too heavy for the ventilators
    - Switched to 2L bags--completed March 2016
- Malignant Hyperthermia kits
  - Contain 1L Sterile Water bags for reconstitution of dantrolene
  - Not enough room for 2L bag
  - Kits are locked in 3 OR locations
    - Kit locks are checked daily by pharmacy tech and monthly by pharmacist
    - Pharmacist is notified when kit is used to aid in preparation



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How does your institution make sure the right ingredients in the right amounts are added to IV bags/ syringes during sterile IV preparation?

- A. Syringe pull back method
- B. Pharmacist watching IV preparation process
- C. IV workflow software (use of cameras/ barcode scanning)
- D. IV robot



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**BEST PRACTICE 11:** When compounding sterile preparations, perform an independent verification to ensure that the proper ingredients (medications and diluents) are added, including confirmation of the proper amount (volume) of each ingredient prior to its addition to the final container.

**IV workflow software:**

- Displays key preparation details, including dose calculations, preparer, products used, lot numbers and expiration dates
- Visualization of each preparation step (camera/pictures)
- Includes barcode scanning of all products used in preparation



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**BEST PRACTICE 11: Sterile IV Preparation**

- Barriers to Best Practice #11
  - Cost of IV workflow management systems
  - Resources
    - Pharmacist to staff IV room at all times
    - Time for training all staff to use the IV workflow software
  - Space for cameras, computers
  - Technology
    - Resources to implement and support new systems



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## BEST PRACTICE 12: Eliminate the prescribing of fentaNYL patches for opioid-naïve patients and/or patients with acute pain.

fentaNYL (DURAGESIC) 50 mcg/hr 72 hr patch 50 mcg

New

☒ Edit Clinical & Dispensing Information

Order dose:	50 mcg	Route:	Transdermal	Frequency:	EVERY 72H
Admin dose:	50 mcg (1 Patch)	Administer over:	72 Hours	For:	30 Days
				# of doses:	10
				1st dose:	Today 1330

BestPractice Advisory - Test, Ann J

Fentanyl patches are restricted to opioid tolerant patients and may be used inpatient if initial dose is 12 mcg/hr or 25 mcg/hr and the patient is receiving other opioid agents, scheduled or PRN, equal to at least 60 mg of oral morphine in 24 hour period for at least 7 days and 1 of the following 3 criteria is met: 1.) Fentanyl patch was prescribed at home 2.) Patient is being followed by either Palliative Care or the Anesthesia Pain services 3.) A Clinical Pharmacy Specialist, in collaboration with the primary service, is involved in the recommendation and is consistently following the service that is caring for the patient. **Click CANCEL to remain in order to verify appropriateness.**

☒ Edit Admin Instructions & Note to Pharm

Admin instructions:  
Remove old patches. Do not cut patch.  
FOLD AND FLUSH DOWN TOILET.

To do—ability to document the patient's opioid status in the health record

- Have this information easy to find when prescribing

## BEST PRACTICE 13: Eliminate injectable promethazine from the hospital.

- Removed the promethazine 50 mg/mL strength in October 2006
  - After the ISMP alert describing life and limb-threatening extravasations
- Later removed the 25 mg/mL in January 2007

## BEST PRACTICE 14: Seek out and use information about medication safety risks and errors that have occurred in other organizations outside of your facility, and take action to prevent similar errors

ISMP Medication Safety Alert: Action Agenda

No.	Problem	Recommendation	Organization Assessment	Action Required/Assignment	Date Completed
(1)	Overdoses are possible when misprogramming infusions with custom concentrations that do not employ a hard minimum concentration alert. Accidentally programming a lower concentration than the actual product concentration results in the delivery of a higher dose than prescribed since more volume will be infused. A "low concentration" alert from smart pumps has been misinterpreted as a "low dose" alert and thought to be inconsequential. Without a hard minimum concentration limit, errors due to the misprogramming of an infusion pump can lead to life-threatening events.	Custom concentrations without a hard "low concentration" alert can lead to overdoses. We do have some intermittent alerts, entries with no hard minimum concentration limit, and the difference between "low concentration" and "low dose" alerts. If a custom concentration is needed, set a hard minimum concentration limit. Use distinctive labels to distinguish custom concentrations. Express the drug concentration on the label and medication administration record (MAR) the same way as entered into the pump (e.g., mg/mL, total drug/total volume).	Pharmacy intern project to determine medications that need hard min conc limit added.		
(2)	When treating hyperkalemia, errors have occurred due to measuring intravenous (IV) insulin doses in mL instead of units, not using an insulin syringe to measure doses, and lack of an independent double check during emergencies. During a code, a pharmacist accidentally withdrew 100 units (instead of 10 units) of insulin into a 3 mL syringe and added it to 50 mL of 50% dextrose.	Develop hyperkalemia treatment protocols that define interventions and monitoring. Outside of emergencies, require the use of standard order sets that automatically populate the correct insulin dose and route. Have pharmacy prepare all insulin doses or supply a hyperkalemia kit with a 3-gauge compatible needleless insulin syringe. Require an independent double check of IV insulin doses and correct administration to those with doses.	All IV regular insulin (from adult and PEDs hyperkalemia order set) doses are dispensed from CTA/PEDs pharmacy as diluted (0.5 units/mL). Epic hyperkalemia order set includes the insulin type, dose, and route.		

To do—share this information with all staff

What are some of the barriers at your institution in implementing the ISMP Best Practices?

## Barriers to implementation

- Staff and/ or management do not perceive a risk with current workflow
- Resources to work on each of the Best Practice projects
- Limitations with the electronic health record
  - Computer system itself cannot support the change
  - Not enough IT support to work on the project
  - Competing resources for the IT support
- Not happy with partial implementation
- Not sure how to implement the best practice without technology
- Space/ equipment limitations
  - Enough physical space, refrigerator space



## ISMP Best Practices for 2018-2019: Are we there yet?

### Post-test Questions

1. Which are examples of ISMP Best Practices for 2018-2019.
  - A. Provide patient education for all warfarin discharge orders.
  - B. Eliminate glacial acetic acid from all areas of the hospital.
  - C. Avoid the use of stated, estimated, or historical weights.
  - D. B and C
2. Lack of leadership buy-in, cost and technology are barriers to implementing the ISMP Best Practices.
  - A. True
  - B. False
3. The ISMP Best Practices have been fully implemented in greater than 90% of hospitals.
  - A. True
  - B. False
4. Some ways to segregate, sequester and differentiate all neuromuscular blocking agents from other medications, wherever they are stored in the organization, include:
  - A. Use of lidded bins
  - B. Use of cubies or lock-lidded bins in Pyxis
  - C. Store neuromuscular blocking agents in alphabetical order on shelves
  - D. Add an auxiliary sticker stating "Warning: Paralyzing Agent—causes respiratory arrest, patient must be ventilated" to bins where these are stored
  - E. A and B
  - F. A, B, and D
5. Vincristine should be prepared in minibags instead of an IV syringe to avoid what safety issue?
  - A. Patients receiving the medication on a daily basis instead of a weekly basis
  - B. Patients receiving the medication as an intrathecal injection instead of an IV injection
  - C. Patients receiving the medication dosed using the wrong weight
  - D. Patients receiving the medication infused at the wrong rate



## Clinical Pearls 2018

Kevin Bacigalupo, Pharm.D., BCPS, BCGP  
James C. Lee, Pharm.D., BCACP  
Nick Van Hise, Pharm.D., BCPS



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## Directions to De-prescribing in Older Adults



Kevin Bacigalupo Pharm.D., BCPS, BCGP  
Clinical Pharmacy Specialist - Geriatrics



I have no actual or potential conflicts of interest to disclose.  
I am not here as a representative of the VA and any opinions expressed are my own and do not necessarily represent the views of the Department of Veterans Affairs or the United States of America



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## Learning Objectives for Pharmacists

Discuss risks of polypharmacy in older adults and approaches to de-prescribe in this population

Review updated tools to assist with safe prescribing in older adults



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## Polypharmacy

- 44% of men and 57% of women aged 65+ take  $\geq 5$  medications per day!
- Over 50% of older adults use at least 1 OTC medication daily
- Nearly 2/3 of older adults use at least one dietary supplement daily
- 15% of older adults use a combination of drugs at risk for a major drug interaction

Qato, DM et al., *JAMA Intern Med*. 2016 April ; 176(4): 473-482



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## Why are Older Adults at risk for Medication-Related Problems?

### Medication Multipliers

- High # of chronic diseases
- Numerous prescribers
- Frequent use of OTC meds
- Multiple pharmacies
- Increased use of high risk medications

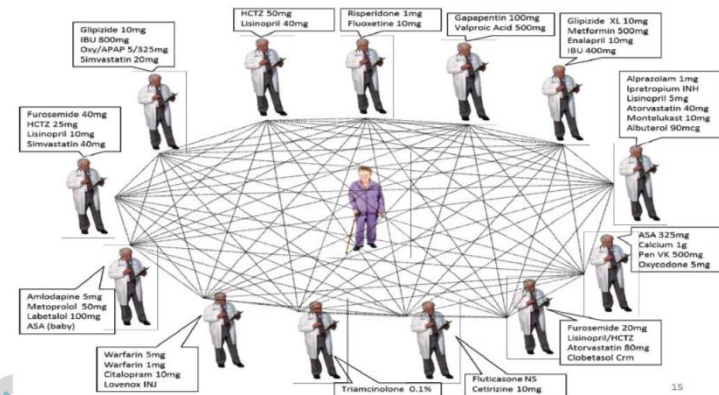
### Additional Risk Factors

- Lack of trained professionals in geriatrics
- Underrepresented in trials
- Pharmacokinetic changes
- Pharmacodynamic changes
- Memory impairment

ELEVATE

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## Will the real prescriber please stand up...



15

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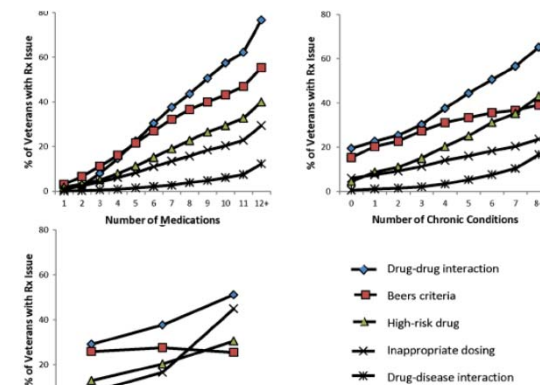
## Risks of Polypharmacy

- Adverse Drug Events
- Falls
- Hospitalizations
- Mortality
- Decline in Cognition
- Decline in Function



Fried, TR et al., J Am Geriatr Soc. 2014 December ; 62(12): 2261-2272

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Steinman MA et al., J Gen Intern Med. 2014 March; 29(10):1379-86

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## De-prescribing Defined

The planned and supervised process of

DOSE REDUCTION or STOPPING

of medication that may be

CAUSING HARM  
and/or

NO LONGER PROVIDING BENEFIT

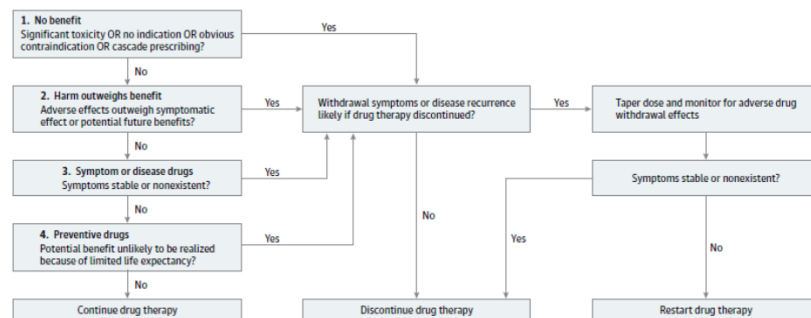


## 3 steps to De-prescribing

1. Perform a comprehensive medication review  
(Appropriateness/Adherence/Adverse Drug Reactions)
2. Match medications to medical conditions/diagnoses
3. Identify and discontinue unnecessary & inappropriate medications

## The Process of De-prescribing

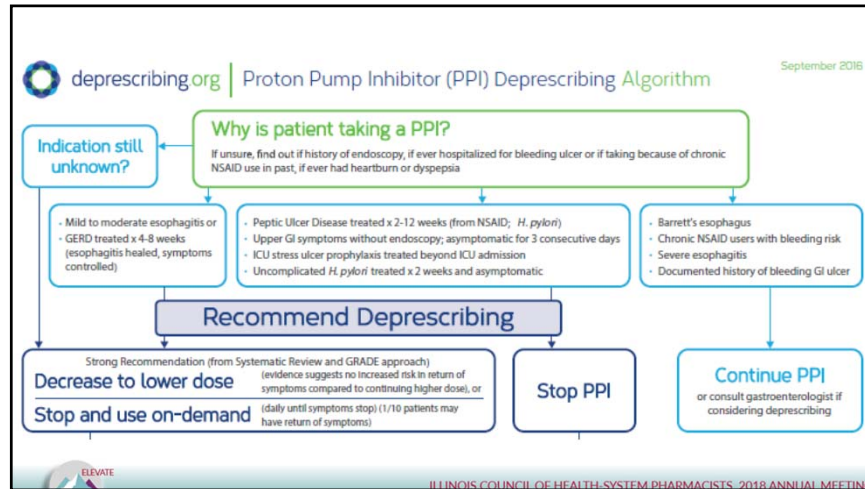
Figure. Algorithm for Deciding Order and Mode in Which Drug Use Could Be Discontinued



Scott I et al., JAMA Internal medicine, 2015; 175(5), 827-834.

## De-prescribing

- IF the medication is not effective or not indicated  
**STOP the medication**
- IF the medication is overprescribed  
**STOP the medication or DECREASE the dose**
- IF the medication causes current symptoms  
**DECREASE the dose or SWITCH to a safer alternative**
- IMPLEMENT Non-pharmacologic approaches
- IF the medication is potentially inappropriate  
**SWITCH to a safer alternative**



MedStopper

Stopping Priority RED=Highest GREEN=Lowest	Medication/ Category/ Condition	May Improve Symptoms?	May Reduce Risk for Future Illness?	May Cause Harm?	Suggested Taper Approach	Possible Symptoms when Stopping or Tapering	Beers/STOPP Criteria
Orange box	alprazolam (Xanax) / Benzodiazepine / Insomnia	Blue sad face	Red sad face	Red sad face	If used daily for more than 3-4 weeks: Reduce dose by 25% every week (i.e. week 1-75%, week 2-50%, week 3-25%) and this can be extended or decreased (10% dose reductions) if needed. If intolerable withdrawal symptoms occur (usually 1-3 days after a dose change), go back to the previously tolerated dose until symptoms resolve and plan for a more gradual taper with the patient. Dose reduction may need to slow down as one gets to smaller doses (i.e. 25% of the original dose). Overall, the rate of discontinuation needs to be controlled by the person taking the medication.	rebound insomnia, tremor, anxiety, as well as more serious, rare manifestations including hallucinations, seizures, and delirium	Details

Available at: <http://medstopper.com/>. Accessed August 11, 2018

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## Case

- BO is an 86 y/o male who presents to the geriatrics clinic for the first time with his wife
- He is interested in reducing medication costs and burden
- He has had 3 falls in the past 2 months during the mid-day hours
- Wife is concerned with more unsteady gait and worsening cognition in the past month
- No dizziness or lightheadedness. (+) BLE peripheral neuropathy that impairs ability to get a good nights sleep. He had a cough 3 weeks ago and went to a Minute Clinic and this is now improved. No other complaints

## Case

**PMH:** CAD s/p CABG 2010, hyperlipidemia, HTN, BPH, GERD, peripheral neuropathy, DJD s/p L hip replacement 10 yrs. ago and R knee replacement ~20 yrs. ago, insomnia

**Pertinent Labs:** Scr 1.1, LDL 82, HDL 61, Trigs 76  
-all other relevant labs are wnl

**Vitals:** 125/80, HR 66 bpm, RR 18, pain score is 3

## Reconciled Med List

- Aspirin 81mg EC daily
- Clopidogrel 75mg daily
- Finasteride 5mg daily
- Fish oil 500mg daily
- Gabapentin 400mg bid
- Pantoprazole 40mg qam
- Simvastatin 40mg qbedtime
- Tamsulosin 0.4mg qbedtime
- Tramadol 50mg q8h PRN for pain
- Metoprolol SA 50mg daily
- Clorazepate 7.5mg qbedtime
- Codeine/Guaifenesin 10mg/100mg q6h PRN cough
- Dicyclomine 10mg tid with meals



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## Which of BO's medications would you put the highest priority on de-prescribing?

- A. Clorazepate 7.5mg qbedtime
- B. Clopidogrel 75mg daily
- C. Dicyclomine 10mg tid with meals
- D. Fish Oil 500mg daily
- E. Codeine/Guaifenesin 10/100mg q6h PRN for cough



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## Beers Criteria 2018



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### Original Beers Criteria – 1991

- Explicit criteria for determining inappropriate medication use in nursing home residents

1997

- Expanded to all adults older than 65 years

2003

2012

- American Geriatrics Society took ownership

2015

- Added renal dose adjustments table, drug interaction table, companion papers (how to use; alternatives)

2018



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## What is the Purpose of the Beers Criteria?

- Identify potentially inappropriate medications that should be avoided in many older adults
- Reduce adverse drug events and drug related problems
- Improve medication selection in older adults
- Designed for use in any clinical setting; also used as an educational, quality, and research tool
  - Not applicable to hospice and palliative care

## Beers Criteria – Key Tables

- **Table 2** – Potentially inappropriate drugs to avoid
  - Organized by organ system and therapeutic category
- **Table 3** – Drug-Disease or Drug-Syndrome
  - May exacerbate disease or condition
- **Table 4** – Medications to use with caution
- **Table 5** – Drug-Drug Interactions
  - Non anti-infectives
- **Table 6** – Renal dosing table – No major changes in 2018
  - Non anti-infectives

## Table 2 Changes – Potentially Inappropriate

### Added / Changed

- Metoclopramide – duration update to up to 12 weeks
- Sliding Scale insulin (SSI) language modified

### Removed

- Ticlopidine
- Guanabenz, Guanfacine, Methyldopa, Reserpine (>0.1mg/day)
- Meprobamate
- Ergoloid Mesylates
- Pentazocine

## Table 3 Changes – Drug Disease / Syndrome

### Added / Changed

- SNRI's with h/o falls or fracture
- Reduced opioid level of evidence with falls to MOD
- Add pimavanserin as exception for PD

### Removed

- Chronic seizures or epilepsy as a condition
- Insomnia as a condition
- H2 antagonists with dementia; reduced quality of evidence to LOW for delirium

## Table 4 Changes – Meds to use with Caution

### Added / Changed

- DPP-4 inhibitors with HFrEF
- Dextromethorphan/Quinidine
- Trimethoprim/Sulfamethoxazole in patients on ACEI or ARB with reduced CrCl
- Aspirin for primary CV proph. changed to  $\geq 70$  y/o
- Rivaroxaban  $\geq 75$  y/o

### Removed

- Vasodilators

## Table 5 Changes – Drug Interactions

### Added / Changed

- Opioids/Benzos – overdose risk
- Opioids/Gabapenoids – overdose
- Antiepileptics +  $\geq 2$  CNS drugs
- Warfarin/Ciprofloxacin
- Warfarin/Macrolides
- Warfarin/Trimethoprim/Sulfamethoxazole

### Removed

- ACEI + amiloride or triamterene and changed to:
  - ACEI
  - ARB
  - Aliskerin
- Avoid  $\geq 1$  Potassium raising med
  - K<sup>+</sup> sparing diuretics

## Pop Quiz Hot Shot!

Which of the following is a medication related update in the 2018 Beers criteria?

- Aspirin should be used with caution for primary CV prophylaxis in those  $\geq 80$  y/o
- Venlafaxine use is potentially inappropriate for those with a h/o falls or fracture
- Metoclopramide is potentially inappropriate if used  $\geq 6$  weeks
- Warfarin and amoxicillin is a drug interaction to be avoided in older adults

## Questions?



## References

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## Pharmacogenomics: An Inpatient Perspective

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## Conflict of Interest Declaration

James Lee, PharmD, has no actual or potential conflicts of interest to report.



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## Learning Objective - Pharmacist

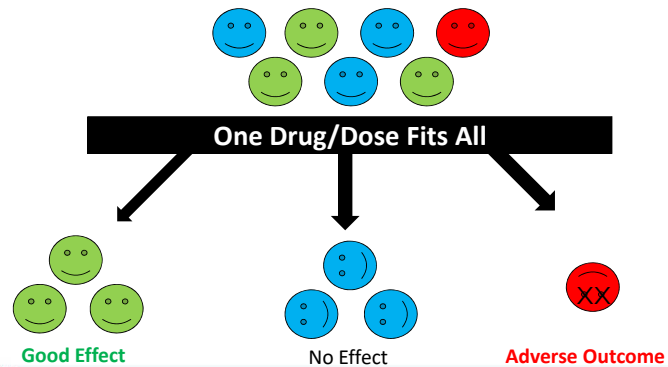
Describe considerations for implementing and applying pharmacogenomics (PGx) testing in the inpatient setting.



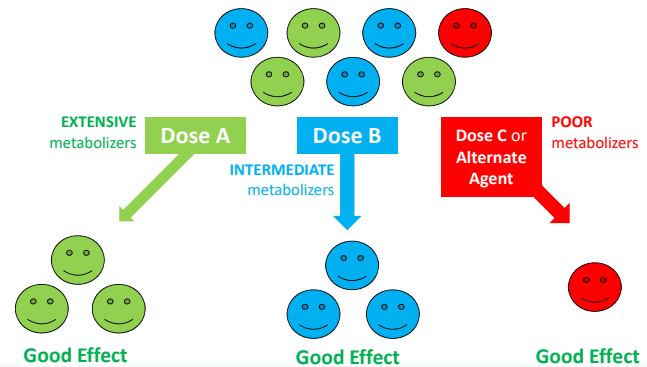
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## Today's Standard Approach



## A Tailored Approach



## Using PGx to choose between therapeutic equals

### Avoid medication-related adverse events and safely achieve optimal treatment outcomes

- Improve treatment safety
- Reduce hospitalizations

### Advance patient understanding of individual health and health risk

- Improve medication adherence

### Reduce medication spending waste

- Reduce care costs associated w/ empiric drug selection and dosing



## Common Gene-Drug Pairs

### Drug Metabolism & Transporter Function

- CYP2D6: TCA/SSRI (dosing/selection), **codeine** (toxicity: conversion to morphine)
- CYP2C9: **warfarin** (w/ VKORC1: dosing), **phenytoin** (w/ HLA-B\*15:02)
- CYP2C19: TCA/SSRI (dosing/selection), **clopidogrel** (bioactivation), **voriconazole** (dosing)
- DPYD: fluoropyrimidines (toxicity)
- TPMT: thiopurines (toxicity)
- SLCO1B1: simvastatin (myopathy)

### Human Leukocyte Antigen Carrier Status → hypersensitivity

- HLA-B\*57:01: abacavir
- HLA-B\*58:01: allopurinol
- HLA-B\*15:02 / HLA-A\*31:01: carbamazepine, oxcarbazepine
- HLA-B\*15:02: phenytoin

## Interpretation, Translation, Intervention



### Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Develops peer-reviewed, expert consensus guidelines
- Evidence from preclinical functional and clinical data, and disease-specific consensus guidelines
- Assist clinicians with **HOW** to **translate** and **apply** test results
- Address implementation process and barriers

## Considerations: It Takes a Team & Commitment

### Support For PGx Within Your Institution

- **Institutional value:** Priority of PGx; Investment/opportunity or a cost?
- **Clinician interest & expertise:** pharmacist, physician, other advanced practitioners
- **Physician champion**
- **Interdepartmental support:** IT build/support, clinical department utilization
- **Support personnel:** administrative, research, student support

**Be prepared for consistent education drives**

## Considerations: Who, What, & How to Test

### Selecting Patients (WHO)

- **Higher risk** patients
- Patient level **suboptimal treatment outcomes**
- **Institutional level outcomes** with room for improvement

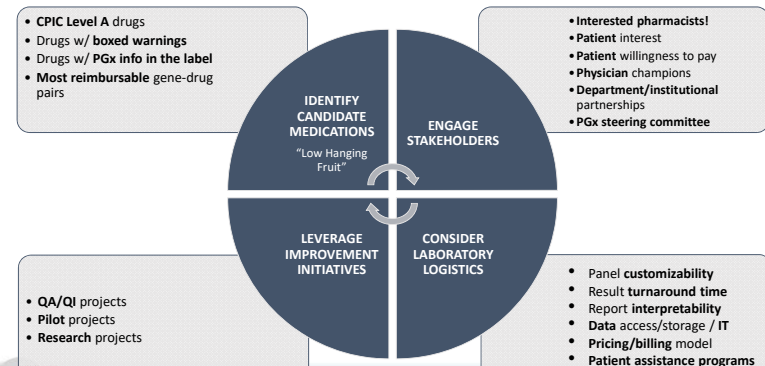
### Testing Approach (WHEN & HOW)

- **Reactive** vs pre-emptive testing
- **Single** gene vs multigene (consider commonly prescribed medications)
- **In-house** vs third party laboratory

### Reimbursement: Billing Model / Cost Perspective

- Will provider bill?
- How is patient billed?
- Focus on **global cost savings** vs revenue generation

## Multi-prong Planning & Implementation



Which of the following should be considered when implementing pharmacogenomics in the inpatient setting?

- A. A multi-pronged approach incorporating internal and outside stakeholders in the planning and implementation process is essential.
- B. Consider implementing pharmacogenomics testing for commonly prescribed medications rated as CPIC Level C.
- C. Pharmacists should lead the effort and solicit feedback from outside the pharmacy department as needed.
- D. CPIC guidelines provide guidance on determining which settings pharmacogenomic testing should be implemented in.



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## Updates on *Clostridium difficile*

Nick Van Hise, PharmD, BCPS  
Infectious Disease Pharmacy Specialist/Research Coordinator  
Metro Infectious Disease Consultants



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## Learning Objectives - Pharmacists

- State *Clostridium difficile* infection (CDI) treatment recommendations consistent with the 2018 IDSA guidelines based on patient-specific factors
- Recall treatment considerations for reducing the risk of *Clostridium difficile* recurrence



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## Potential Conflicts

- Related to Cdiff
  - Principal Investigator for a Phase II Clinical Trial study for FMT funded by Finch Therapeutics
- Unrelated to Cdiff
  - Speaker bureau for antibacterial agents for Melinta, Astellas, and Merck

All conflicts were resolved through peer review



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## Background

- *C. difficile* is a gram-positive, anaerobic, spore-forming rod
- Leading cause of hospital-acquired diarrhea
- >250,000 cases per year
- \$1.1 billion per year in the United States
- Mortality 1-2.5%
- Complications: toxic megacolon, *C. difficile*-associated arthritis, septicemia

Aslam S, et al. *Lancet Infect Dis.* 2005.  
Brito GA, et al. *J Infect Dis.* 2002.

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## Economic Impact

- Attributable costs per episode: \$3,791 - \$4,846
- Annual US healthcare costs: \$433 - \$797 M
- Overall costs per hospitalization case-control
  - 85% higher costs for CDI (\$55K vs. \$28K)
  - 99% longer length of stay (21.1 vs 10 days)
- Special populations per episode
  - Recurrent: \$13,655 - \$18,067
  - IBD, surgical inpatient, ICU: \$90K

Kyne L, et al. *Clin Infect Dis.* 2002.  
Dubberke ER, et al. *Clin Infect Dis.* 2008.  
Ghantaji SS, et al. *J Hosp Infect.* 2010.  
Pakyz A, et al. *Pharmacother.* 2011.

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## Pathogenesis

- 3 events must occur for the development of *C. difficile* infection (CDI)
  1. Disruption of normal intestinal flora
  2. Exposure to *C. difficile*
  3. Inadequate host immune response

Owens RC, et al. *Clin Infect Dis.* 2008.  
Howell MD, et al. *Arch Intern Med.* 2010.  
Kelly CP, et al. *NEJM.* 2008.

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## Diagnosis

- Onset usually 1-2 days after antibiotic initiation
- Can be as long as 10 weeks after discontinuation of antibiotic
- Diagnosis:
  - Diarrhea ( $\geq 3$  unformed stools/24 hrs for  $\geq 2$  days)
  - PLUS Positive *C. difficile* toxin in stool sample
  - OR pseudomembranes seen in the colon
- Colonization versus infection
  - NAAT
  - Toxin
  - GDH
- The key is symptoms:  $\geq 3$  bouts of diarrhea in a 24 hour period

Peterson LR, et al. *Ann Intern Med.* 2009.  
McDonald LC, et al. *Clin. Inf. Diseases.* 2018.  
Bobo LD, et al. *Chest.* 2011.

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## Acquisition of *Clostridium difficile*

- Acquisition usually in hospital
- Commonly cultured from inanimate objects
- Can persist for 40 days
- Acquisition rate 13% with a stay of 2 weeks and 50% when stay > 4 weeks
- Share a room → 3.2 days

Schroeder, MS. *Am Fam Physician*, 2005;71:921-28.

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## Initial Mild to Moderate CDI Treatment

- Previous guidelines recommended metronidazole as first line therapy
- Update removed metronidazole from the guidelines
- First therapy:
  - Oral Vancomycin for 10 days
  - Fidaxomicin for 10 days
- Caveats:
  - Accessibility of vancomycin or fidaxomicin is not an option, metronidazole can be considered for mild to moderate CDI
  - Fidaxomicin should be considered over vancomycin in pts at high risk for recurrence

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

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66yo WF presents with intra-abdominal infection secondary to diverticulitis. Patient rapidly improved with fluids and IV antibiotics. Pt discharged on augmentin to finish a 7 day course. Upon discharge, the patient begins to have diarrhea with 6-7 bouts of diarrhea a day and is PCR positive for Cdiff.

What is the most appropriate therapy?

- Metronidazole PO 500mg every 8 hours for 10 days
- Vancomycin 125mg PO QID (four times daily) for 10 days
- Vancomycin 250mg PO QID (four times daily) for 10 days
- Fecal Microbiota Transplant

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## Initial Severe to Fulminant Treatment

- Severe:
  - Vanco 125mg every 6 hours OR
  - Fidaxomicin 200mg BID
- Fulminant:
  - Vanco 500mg every 6 hours PO or NG PLUS metronidazole IV 500mg every 8 hours
  - Rectal instillation of vanco every 6 hours should be considered in situations of ileus (500mg in 1L NS)

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

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## Severe CDI

- Vancomycin 500mg PO every 6 hours
- Fidaxomicin 200mg every 12 hours
- Fulminant CDI: standard of care for severe plus
  - If ileus, consider rectal instillation of vancomycin
  - Metronidazole 500mg IV every 8 hours

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

## Demotion of Metronidazole

- Higher cure rates with vancomycin compared to metronidazole
- Increased resistance with metronidazole to clostridium difficile isolates
- MIC<sub>90</sub> 0.25-1 mcg/mL
- Resistance: 6%
- Rapid oral absorption (6-15% in stool)
- Stool concentrations
  - 9.3 ± 7.5 ug/g (wet)
  - 1.2 ug/g (formed)
- Failures
  - Decreased mucosal inflammation?
  - Increased absorption?
  - MIC drift?
  - Poor concentration/MIC ratios

Chow AW, et al. *Antimicrob Agents Chemother*. 1985.  
Pelaez T, et al. *Antimicrob Agents Chemother*. 2002.  
Bolton RP, et al. *Gut*. 1986.

Which of the following are reasons for why metronidazole was removed from the first line treatment of mild to moderate CDI (Cdiff infection)?

- Metronidazole resistance
- Poor concentration/MIC ratios due to MIC drift
- High cost of metronidazole
- Lack of availability of metronidazole
- A&B
- All of the above

## Other Dosage Schemes for Recurrence

- Vancomycin tapered pulse:
  - 125mg PO q6 for 10 to 14 days
  - 125mg PO q12 for 7 days
  - 125mg PO once daily for 7 days
  - 125mg PO every 2 or 3 days for 2 to 8 weeks
- Fidaxomicin 200mg PO BID
- Fidaxomicin 200mg BID on days 1-5, then once daily on alternate dates on days 7-25\*

\*Not yet in IDSA guidelines

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.  
Guery, et al. *The Lancet Infectious Diseases*. 2018.

## Recurrent CDI Treatment

- Tapered pulse vancomycin
- Pulse fidaxomicin
- Fecal Microbiota Transplant (FMT)
- Bezlotoxumab (Zinplava®)

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

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## Fecal Microbiota Transplant (FMT)

- Single healthy donor with necessary screening performed
- Healthy, monogamous donor → criteria not specified in IDSA guidelines
  - Refer to FDA Guidance of 2016 to criteria to meet for FMT
- Various pharmaceutical company FMT products
  - Seres Pharma. ®
  - Rebiotix®
  - Finch Therapeutics® (working with OpenBiome®)

Gough E, et al. *Clin Infect Dis*. 2011.  
Kelly CR, et al. *J Clin Gastroenterol*. 2012.  
Kao D, et al. *JAMA*. 2017.

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## Prevention of Recurrence

- Antimicrobial Stewardship
  - Minimize frequency, duration of high risk antibiotics
  - Implement a coordinated stewardship program following IDSA/SHEA Stewardship Update of 2016
  - Restrictions of specific classes that are associated with highest rates of CDI
  - PPI restriction

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

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## Prevention of Recurrence

- Oral vancomycin prophylaxis
  - Should be considered in high risk patients on broad spectrum antibiotics who have a history of CDI
  - If previous CDI even was greater than 1 year ago, evidence is weaker
  - Dosage varies between 125 to 250mg daily to BID → likely should be based upon pts baseline bowel movement status
- High risk criteria to consider:
  - Time since last recurrence
  - Severity of previous recurrences
  - Hx. of FMT or bezlotoxumab
  - Frailty of patient

McDonald LC, et al. *Clin. Inf. Diseases*. 2018.

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THANK YOU FOR  
LISTENING!  
QUESTIONS OR  
COMMENTS?





# Updates in Diabetes and Cardiovascular Disease Management: Are You Making the Link?

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**Jennifer D'Souza, PharmD, CDE, BC-ADM<sup>1</sup>**

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*The speakers have no actual or potential conflicts of interest in relation to this activity.*

## Learning Objectives - Pharmacist

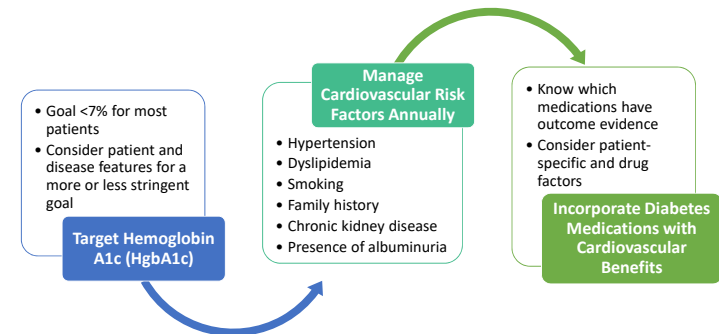
- Apply recent changes to blood pressure goals in patients with diabetes
- Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events
- Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes

## Cardiovascular Risk and Diseases in Diabetes

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in a patient with diabetes mellitus (DM)
- Largest contributor to direct and indirect costs
- Hypertension (HTN) and dyslipidemia are clear risk factors for ASCVD in patients with diabetes

American Diabetes Association. Diabetes Care. 2018;41(Suppl 1):S73-S85.

## Making the Link in Clinical Practice



American Diabetes Association. Diabetes Care. 2018;41(Suppl1):S55-S64.  
American Diabetes Association. Diabetes Care. 2018;41(Suppl1):S73-S85.

## Learning Objectives - Pharmacist

- **Apply recent changes to blood pressure goals in patients with diabetes**
- Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events
- Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes



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## Hypertension and Diabetes

- Approximately 80% of adult DM patients have HTN
- Co-existence of HTN and DM significantly increases risk of:
  - Coronary heart disease
  - Stroke
  - Heart failure
  - Peripheral arterial disease
  - Cardiovascular mortality
  - Nephropathy
  - Retinopathy
- Limited quality evidence regarding optimal blood pressure goal in DM
- Many changes over recent years based on new evidence

Whelton PK, Carey RM, et al. *J Am Coll Cardiol.* 2018; 71(19):e127-e248.

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## Guideline Comparison of Blood Pressure Goals

Guideline	General HTN (mmHg)	Diabetes (mmHg)
JNC7 (2003)	<140/90	<130/80
JNC8 (2014)	<140/90	<140/90
ADA (2014)	N/A	<140/80 (<130 if undue burden)
ADA (2015)	N/A	<140/90
ACC/AHA (2017)	<130/80	<130/80
ADA (2018)	N/A	<140/90 (<130 if high CV risk)

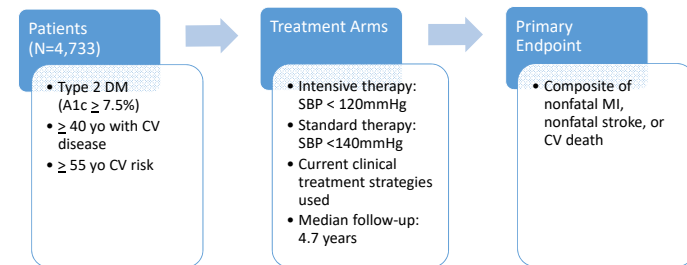
Chobanian AV, et al. *JAMA.* 2003; 289(19): 2560-71.  
 American Diabetes Association. *Diabetes Care.* 2014;37(Suppl. 1):S5-S13.  
 James PA, et al. *JAMA.* 2014; 311(5):507-520.  
 American Diabetes Association. *Diabetes Care.* 2015;38(Suppl. 1):S49-S57.  
 Whelton PK, et al. *J Am Coll Cardiol.* 2018; 71(19):e127-e248.  
 American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S86-S104.



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## ACCORD BP

- The Action to Control Cardiovascular Risk in Diabetes blood pressure trial



CV= cardiovascular; MI= myocardial infarction; SBP= systolic blood pressure

The ACCORD Study Group. *N Engl J Med.* 2010; 362:1575-85.

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## ACCORD BP Results

- Patients: 62.2 years, 47.7% women, 33.7% CV disease
  - Baseline BP: 139.2/76 mmHg
- SBP at 1 year:
  - Intensive (119.3 mmHg) vs Standard (133.5 mmHg)

Outcome	Intensive Therapy (N=2363) N(%/year)	Standard Therapy (N=2371) N(%/year)	Hazard Ratio (95% CI)	P Value
Primary*	208 (1.87)	237 (2.09)	0.88 (0.73-1.06)	0.20
Nonfatal MI	126 (1.13)	146 (1.28)	0.87(0.68-1.10)	0.25
Any Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.96)	0.03
CV Death	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74

The ACCORD Study Group. *N Engl J Med.* 2010; 362:1575-85.

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## 2018 ADA Recommendations

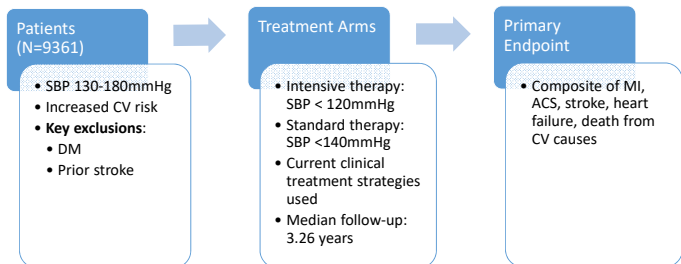
- At a minimum, treat to <140/90 mmHg to reduce CV and microvascular complications
- Lower goals (<130/80 or <120/80) may be beneficial if high CV risk
  - History of stroke
  - CV disease
  - Albuminuria
- Treatment goals should be individualized
- Pharmacologic treatment based on presence of albuminuria (>30mg/g)
  - Albuminuria: ACEi or ARB
  - Without albuminuria: ACEi, ARB, thiazide, calcium channel blocker
    - Proven reduction in CV events in DM patients

American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S86-S104.

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## SPRINT

- A Randomized Trial of Intensive versus Standard Blood-Pressure Control



ACS= acute coronary syndrome; CV= cardiovascular; MI= myocardial infarction; SBP= systolic blood pressure

The SPRINT Research Group. *N Engl J Med.* 2015;373:2103-2116.

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## SPRINT Results

- Patients: 67.9 years, ~35% women, 20% CV disease
  - Baseline BP: 139.7/78 mmHg
- SBP at 1 year:
  - Intensive (121.4 mmHg) vs Standard (136.2 mmHg)

Outcome	Intensive Therapy (N=4678) N(%/year)	Standard Therapy (N=4683) N(%/year)	Hazard Ratio (95% CI)	P Value
Primary*	243 (1.65)	319 (2.19)	0.75 (0.64-0.89)	<0.001
MI	97 (0.65)	116 (0.78)	0.83 (0.64-1.09)	0.19
ACS	40 (0.27)	40 (0.27)	1.00 (0.64-1.55)	0.99
Heart Failure	62 (0.41)	100 (0.67)	0.62 (0.45-0.84)	0.002
CV Death	37 (0.25)	65 (0.43)	0.57 (0.38-0.85)	0.005
All Cause Death	155 (1.03)	210 (1.40)	0.73 (0.60-0.90)	0.003

The SPRINT Research Group. *N Engl J Med.* 2015;373:2103-2116.

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## 2017 ACC/AHA Recommendations

- Endorse lower BP goals based on SPRINT data
  - Known CVD or 10-year ASCVD risk  $\geq 10\%$ 
    - $<130/80$  mmHg
- Assumes vast majority of patients with DM have 10-year ASCVD risk of  $\geq 10\%$
- Reinforce that ACCORD was underpowered due to lower than expected event rates
- SPRINT sub-study showed patients with prediabetes had similar benefit than those with normoglycemia

Whelton PK, et al. *J Am Coll Cardiol*. 2018; 71(19):e127-e248.

## Summary

- Limited quality evidence available to determine optimal BP target in adults with DM
- Treatment goals should be individualized
- Goal  $<130/80$  mmHg if high risk and tolerated

## Patient Case: Meet SN

A 56-year-old male presents for a follow-up appointment in a pharmacist's diabetes clinic. Upon questioning, he reports taking his medications daily and has no side effects to report. He has a blood glucose log with him which reveals readings  $> 200$  over the past couple of months. He denies symptoms of hypoglycemia.

Past Medical History	Current Medications	Social History	Family History
Type 2 diabetes mellitus Hypertension Hyperlipidemia Peripheral vascular disease	Lisinopril 5 mg PO daily Metformin 1000 mg PO BID Atorvastatin 20 mg PO daily	Former smoker Denies alcohol Denies illicit substances	Father: alive, history of heart disease Mother: died from stroke complications

## Patient Case: Question #1

You assess SN's vitals which were taken at the beginning of his clinic appointment. His BP is 148/86, P 78, RR 14, and T 37.8 °C

According to the 2017 ACC and ADA guidelines, which of the following blood pressure goals is best to target in this patient?

- $< 120/80$  mmHg
- $< 130/80$  mmHg
- $< 140/90$  mmHg
- $< 150/90$  mmHg

## Learning Objectives- Pharmacist

- Apply recent changes to blood pressure goals in patients with diabetes
- **Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events**
- Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes



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## 2008 FDA Guidance for Cardiovascular Risk

- New therapies must not result in an unacceptable increase in CV risk
- Inclusion of major CV events as endpoints in all phase 2 and 3 trials
  - Major CV events (**MACE**): death from CV causes, nonfatal myocardial infarction and nonfatal stroke
- Include high-risk patients for a meaningful estimate of CV risk
- Compare incidence of important CV events occurring with investigational agent versus control group



U.S. Food and Drug Administration. Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available from <https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf>. Accessed 16 July 2018.

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## 2008 FDA Guidance for CV Risk

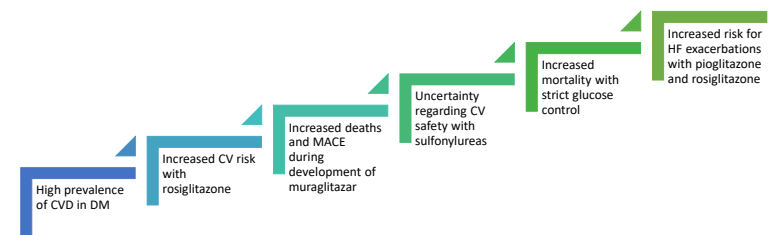
Upper Bound of Two-Sided 95% Confidence Interval for Estimated CV Risk Ratio (investigational drug vs. control)	
> 1.8	<b>Decision:</b> Approval denied <b>Next Steps:</b> Additional, large safety trials should be conducted
1.3-1.8	<b>Decision:</b> Approval granted as overall risk-benefit analysis supports approval <b>Next Steps:</b> Postmarketing trial generally necessary to definitely show estimated risk ratio is < 1.3
< 1.3	<b>Decision:</b> Approval granted as overall risk-benefit analysis supports approval <b>Next Steps:</b> Postmarketing trial may not be necessary



U.S. Food and Drug Administration. Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available from <https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf>. Accessed 16 July 2018.

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## Why was the guidance created?



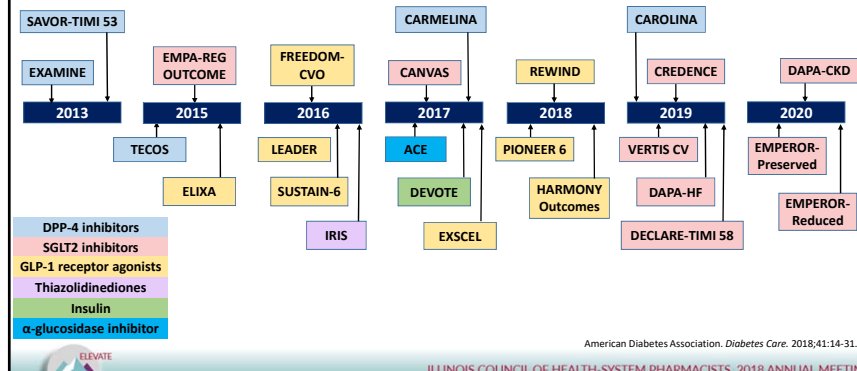
CVD= cardiovascular disease; HF= heart failure

Smith RJ et al. Diabetes Care. 2016;39:738-42.



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## Timeline of CV Outcome Trials in T2DM



## DPP-4 Inhibitors: Summary of CV Risk Trials

Medication/Trial	Saxagliptin / SAVOR-TIMI-53	Alogliptin / EXAMINE	Sitagliptin / TECOS
<b>Control Arm</b>	Placebo	Placebo	Placebo
<b>Design</b>	Randomized, DB, PC 788 sites, 26 countries 16,492 patients	Randomized, DB 898 sites, 49 countries 5380 patients	Randomized, DB, PC 673 sites, 38 countries 14,735 patients
<b>Type 2 Diabetes Mellitus (T2DM) Population</b>	HgbA1c 6.5-12% (mean, 8%) History of CVD (78%) OR multiple risk factors for CVD	HgbA1c 6.5-11% (mean, 8%) - If on insulin: 7-11% ACS within 15-90 days	Age 50+ HgbA1c 6.5-8% (mean, 7.2%) History of CVD
<b>Primary Composite Endpoint &amp; Results</b>	MACE = not significant (NS)	MACE= NS	MACE <b>plus</b> hospitalization for UA - Per-protocol: SS - Intention-to-treat: NS
<b>Secondary Composite Endpoint &amp; Results</b>	Primary composite <b>PLUS</b> , hospitalization for UA, HF, or coronary revascularization = NS	Primary composite <b>PLUS</b> , urgent revascularization due to UA = NS	MACE, per-protocol: SS MACE, intention-to-treat: NS
<b>Other Notes</b>	Hospitalization for HF $\uparrow$ (HR 1.27)	Non-significant trend in $\uparrow$ HF	None
<b>DPP-4 inhibitors do not have a FDA approved indication to reduce CV mortality and events in patients with T2DM and ASCVD.</b>			

Source: Scirica BM et al. NEJM. 2013;369:1317-26. White WB et al. NEJM. 2013;369:1327-35. Green JB et al. NEJM. 2015;373:232-42.

## SGLT-2 Inhibitors: Summary of CV Risk Trials

Medication	Empagliflozin	Canagliflozin	Danagliflozin
<b>Trial Name</b>	EMPA-REG	CANVAS	DECLARE-TIMI-58
<b>Control Arm</b>	Placebo	Placebo	Placebo
<b>Design</b>	Randomized, DB, PC 590 sites, 42 countries 7028 patients	Randomized, DB, Parallel, PC 667 sites, 30 countries 10,142 patients	Randomized, DB, PC 882 sites, 33 countries 17,160 patients
<b>T2DM Population</b>	HgbA1c ranges: - If no Rx: 7-9% - If stable Rx: 7-10% Established ASCVD BMI $\leq$ 45 kg/m <sup>2</sup> eGFR $\geq$ 30 ml/min/1.73m <sup>2</sup>	HgbA1c 7-10.5% Age $\geq$ 30 with established ASCVD <b>OR</b> Age $\geq$ 50 with $\geq$ 2 CVD risk factors eGFR $\geq$ 30 ml/min/1.73m <sup>2</sup>	HgbA1c 6.5 to $<$ 12% Age $\geq$ 40 with established ASCVD <b>OR</b> $\geq$ 2 CVD risk factors <b>OR</b> Male $\geq$ 55, Female $\geq$ 60 with 1 risk factor CrCl $\geq$ 60 mL/min
<b>All trials had a primary composite endpoint of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke</b>			
<b>Secondary Composite Endpoint</b>	Primary composite <b>PLUS</b> hospitalization for UA	Not applicable	Primary composite <b>PLUS</b> CV death/hospitalization for HF
<b>Duration</b>	2.6 years	188.2 weeks (total study: 8 yrs)	Estimated Completion: 7/18/18

BMI= body mass index; CrCl= creatinine clearance;  
eGFR= estimated glomerular filtration rate

Zinman B et al. NEJM. 2015;373(22):2117-28.  
Neal B et al. NEJM. 2017;377(7):644-57.  
Wiviott SD et al. American Heart Journal. 2018;200:83-89.

## SGLT-2 Inhibitors: Baseline Demographics

	Empagliflozin / EMPA-REG	Canagliflozin / CANVAS
<b>Age (mean-yrs)</b>	63.1	63.3
<b>Duration of Diabetes</b>	$\leq$ 1 year: 2.45% >1-5 years: 15.55% 5-10 years: 24.8% >10 years: 57.2%	13.5 (median-yrs)
<b>Baseline HgbA1c (mean)</b>	8.08	8.2
<b>Established ASCVD – %</b>	99	56
<b>Hypertension – %</b>	NR	90
<b>Prior HF – %</b>	NR	14.4
<b>Current smoker</b>	NR	17.8
<b>BMI – kg/m<sup>2</sup></b>	30.7	32
<b>eGFR – ml/min/1.73m<sup>2</sup></b>	74	76.5

Zinman B et al. NEJM. 2015;373(22):2117-28.  
Neal B et al. NEJM. 2017;377(7):644-57.

## SGLT-2 Inhibitors: Results

	Empagliflozin / EMPA-REG		Canagliflozin / CANVAS	
	HR (95%CI)	P Value	HR (95%CI)	P Value
<b>Primary Composite</b>	0.86 (0.74-0.99)	<0.001* 0.04^^	0.86 (0.75-0.97)	<0.001* 0.02^^
<b>Secondary Composite</b>	0.89 (0.78-1.01)	<0.001* 0.08^^	NA	NA
<b>Death from CV causes</b>	0.62 (0.49-0.77)	<0.001	0.87 (0.72-1.06)	0.24
<b>Nonfatal MI</b>	0.87 (0.70-1.09)	0.23	0.85 (0.69-1.05)	--
<b>Nonfatal stroke</b>	1.24 (0.92-1.67)	0.16	0.90 (0.71-1.15)	--
<b>Death from any cause</b>	0.68 (0.57-0.82)	<0.001	0.87 (0.74-1.01)	0.24
<b>Hospitalization for HF</b>	0.65 (0.50-0.85)	0.002	0.67 (0.52-0.87)	--
<b>Other Study Notes</b>	↓ progression of renal disease (p < 0.001)		↑↑ risk of amputation (HR 1.97) ↑ fracture risk (HR 1.26) ↓ progression of renal disease (p < 0.001)	
<b>FDA Approved Indication?</b>	YES		NO	

Zinman B et al. *NEJM*. 2015;373(22):2117-28.  
Neal B et al. *NEJM*. 2017;377(7):644-57.

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## GLP-1 Agonists: Summary of CV Risk Trials

Medication	Lixisenatide	Liraglutide	Semaglutide	Exenatide
<b>Trial Name</b>	<b>ELIXA</b>	<b>LEADER</b>	<b>SUSTAIN-6</b>	<b>EXSCEL</b>
<b>Control Arm</b>	Placebo	Placebo	Placebo	Placebo
<b>Design</b>	Randomized, DB, PC 49 countries 6068 patients	Randomized, DB, PC 410 sites, 32 countries 9340 patients	Randomized, DB, PC, PG 230 sites, 20 countries 3297 patients	Randomized, DB, PC 687 sites, 35 countries 14,752 patients
<b>T2DM Population</b>	ACS event within 180 days	HgbA1c ≥7% Age ≥50 + ≥1 CVD <b>OR</b> Age ≥60 + ≥1 CV risk factor	HgbA1c ≥7% Age ≥50 + ≥1 CVD <b>OR</b> Age ≥60 + ≥1 CV risk factor	HgbA1c 6.5-10% Any level of CV risk - 30% no CV events - 70% CV events
<b>Primary Composite Endpoint</b>	CV death, nonfatal MI, nonfatal stroke, UA	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke
<b>Secondary Composite Endpoint(s)</b>	1. Primary composite or hospitalization for HF 2. Above <b>PLUS</b> coronary revascularization	Primary composite <b>PLUS</b> coronary revascularization, hospitalization for UA or HF	Primary composite <b>PLUS</b> coronary revascularization, hospitalization for UA or HF	<i>Not applicable</i>
<b>Duration</b>	25 months	3.8 years	2.1 years	3.2 years

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## GLP-1 Agonists: Baseline Demographics

	Lixisenatide / ELIXA	Liraglutide / LEADER	Semaglutide / SUSTAIN-6	Exenatide / EXSCEL
<b>Age (mean-yrs)</b>	60.3	64.3	64.6	62
<b>Duration of Diabetes (median-yrs)</b>	9.3	12.8	13.9	12
<b>Baseline HgbA1c (mean)</b>	7.6	8.7	8.7	8
<b>Established ASCVD- %</b>	--	81.4	72.1	73.1
<b>Hypertension - %</b>	76.4	--	92.8	--
<b>Prior HF - %</b>	22.4	17.8	23.6	16.2
<b>Current smoker</b>	11.7	--	NR	11.7
<b>Qualifying ACS Event - %</b>		Not applicable	Not applicable	Not applicable
NSTEMI	38.6			
STEMI	43.9			
Unstable angina	17.2			

NSTEMI= non-ST-elevation myocardial infarction;  
STEMI= ST-elevation myocardial infarction

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Marso SP et al. *NEJM*. 2016;375(19):1834-44.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## GLP-1 Agonists: Results

	Lixisenatide / ELIXA		Liraglutide / LEADER		Semaglutide / SUSTAIN-6		Exenatide / EXSCEL	
	HR (95%CI)	P Value	HR (95%CI)	P Value	HR (95%CI)	P Value	HR (95%CI)	P Value
<b>Primary Composite</b>	1.02 (0.89-1.17)	0.81	0.87 (0.78-0.97)	0.01	0.74 (0.58-0.95)	<0.001* 0.02^^	0.91 (0.83-1.00)	<0.001* 0.061^^
<b>Secondary Composite(s)</b>	0.97 (0.85-1.10) 1.00 (0.90-1.11)	0.63 0.96	0.88 (0.81-0.96)	0.005	0.74 (0.62-0.89)	0.002	--	--
<b>Death from CV causes</b>	0.98 (0.78-1.22)	0.85	0.78 (0.66-0.93)	0.007	0.98 (0.65-1.48)	0.92	0.88 (0.76-1.02)	0.628
<b>Nonfatal MI</b>	1.03 (0.87-1.22)	0.71	0.88 (0.75-1.03)	0.11	0.74 (0.51-1.08)	0.12	0.95 (0.84-1.09)	0.628
<b>Nonfatal stroke</b>	1.12 (0.79-1.58)	0.54	0.89 (0.72-1.11)	0.30	0.61 (0.38-0.99)	0.04	0.86 (0.70-1.07)	0.628
<b>Death from any cause</b>	0.94 (0.78-1.13)	0.50	0.85 (0.74-0.97)	0.02	1.05 (0.74-1.50)	0.79	0.86 (0.77-0.97)	--
<b>Hospitalization for UA</b>	--	--	0.98 (0.76-1.26)	0.87	0.82 (0.47-1.44)	0.49	--	--
<b>Hospitalization for HF</b>	0.96 (0.75-1.23)	0.75	0.87 (0.73-1.05)	0.14	1.11 (0.77-1.61)	0.57	0.94 (0.78-1.13)	--
<b>Hospitalization for coronary revascularization</b>	--	--	0.91 (0.80-1.04)	0.18	0.65 (0.50-0.86)	0.003	--	--
<b>Other Study Notes</b>			↓ progression of renal disease (p 0.003)		↓ progression of renal disease (p 0.005)			
<b>FDA Approved Indication?</b>	NO		YES		NO		NO	

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## Study Critique and Future Considerations

### Limitations

- Lack of generalizability
- Short timeline for assessing potential benefits and harm
- Placebo-controlled design

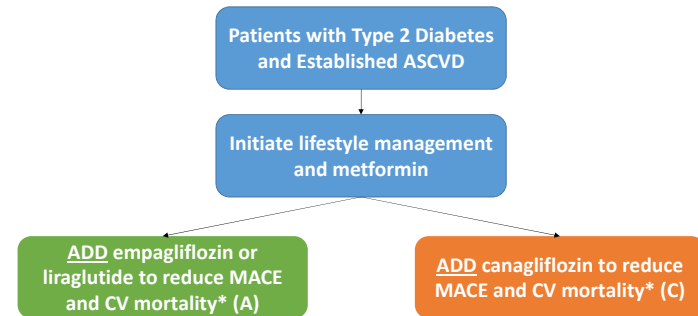
### Considerations for Future Trials

- More diverse, lower-risk populations
- Longer follow-up
- Active comparators
- Innovative designs
- Standardized definitions for safety of microvascular outcomes
- Modifications of end points and analyses
- Establishment of biorepositories
- Enhanced efficacy and cost-sharing options
- Involvement of patients and advocacy organizations

American Diabetes Association. Diabetes Care. 2018;41:14-31.

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## 2018 Standards of Care Recommendations



\*= Consider patient and drug-specific factors in decision making

American Diabetes Association. Diabetes Care. 2018;41(Suppl 1):S73-S85.

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## Patient Case: Question #2

SN's baseline hemoglobin A1c 6 months ago was 9.5%. He was initially started on metformin 500 mg PO BID, and titrated to 1000 mg PO BID approximately three months ago. He denies missing any doses. Today, his hemoglobin A1c is 7.8%. He would like to hold off on any injectable agents at this time if possible.

Taking into account his patient-specific factors, which of the following is best to initiate to achieve optimal glycemic control?

- Canagliflozin
- Empagliflozin
- Liraglutide
- Sitagliptin

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## Learning Objectives - Pharmacist

- Apply recent changes to blood pressure goals in patients with diabetes
- Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events
- **Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes**

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## Barriers to Managing CV Risk

- Access
- Complexities in treatment
- Knowledge gaps
- Coordination of care
- Time

Survey looks at barriers, opportunities for managing CV risk in diabetes patients. *Cardiology*, August 2017: 23.

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## Access

- Cost
  - Large concern of both providers and patients
  - Many new medications are non-formulary or are typically on higher tiers for cost
    - Patients often have to decide if they pay their utility bill or their co-pay
  - Using coupon cards works for certain patients
- Prior authorizations
  - While some newer medications can be prescribed via prior authorizations, the process is time-intensive
  - The more difficult it is to get through, the less likely providers are to use it

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## Complexity of Treatment

- Patients have multiple co-morbidities and each disease state may require multiple treatments
- Difficult to implement lifestyle changes, e.g. diet modification, weight loss, and regular exercise
  - Conflicting information exists to patients regarding diet making it even more difficult to implement

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## Gaps in Knowledge

- Clinicians
  - Understanding of new data from recent clinical trials is a huge critical gap
    - If you don't know the data, then you don't practice it
    - Increasing provider understanding should increase "buy-in" on newer therapies
- Patients
  - Trained to use surrogate markers as a measure of how well they are doing
  - Example - LDL
    - Adding a statin medication to patients whose fasting lipid panel is within range presents challenges

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## Coordinated Care

- Coordinating care among providers (cardiology, endocrinology, primary care) presents challenges
- Physicians may be concerned about “stepping on toes”



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## Time

- It takes a good amount of time to spend with patients to discuss the pros/cons of newer therapies
- Many providers just are not given the opportunity to do so given the typical visit is 15-20 minutes to cover more than just diabetes care



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## Issues that may arise while discussing CV outcome with patients

- “My doctor said my cholesterol is fine. Why would I need a medication for cholesterol?”
- Adding a statin to patients whose fasting lipid panel is within range presents challenges
  - Explaining to patients the reasoning behind the addition
  - Helps that high-intensity statin therapy is available at a low cost



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## Patient Concerns with Medications

- “Aren’t there other medications that are cheaper to control my diabetes?”
- Adding a GLP-1 agonist or SGLT-2 inhibitor with good CV data presents challenges
  - Explaining to patients the reasoning behind the addition, the pros/cons of each medication to treat diabetes
  - Discussing long-term benefits of taking a medication with good CV data



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## Adherence

- “I feel fine. Why do I need take my medication if my glucose is within goal range.”
- Explaining the purpose of medications and why it’s important to maintain adherence even if glucose levels are within range



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## Patient Case: Review

SN

- 56-year-old male
- BP 148/86, P 78, RR 14, T 37.8 °C
- Glucose log reveals readings > 200 over the past couple of months
- Hemoglobin A1c: 9.5% (6 months ago); 7.8% (today)

Past Medical History	Current Medications	Social History	Family History
Type 2 DM Hypertension Hyperlipidemia Peripheral vascular disease	Lisinopril 5 mg PO daily Metformin 1000 mg PO BID Atorvastatin 20 mg PO daily	Former smoker Denies alcohol Denies illicit substances	Father: alive, history of heart disease Mother: died from stroke complications



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## Patient Case: Question #3

In the case of SN, what barriers or challenges may arise when optimizing his cardiovascular risk profile?



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Questions?



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# Do We Have This? A Neonatal and Pediatric Emergency Toolkit

Margaret Heger, PharmD, BCPS, BCPPS  
OSF HealthCare Children's Hospital of Illinois  
September 14<sup>th</sup>, 2018

The speaker has no conflicts of interest to disclose.

## Learning Objectives - Pharmacist

- Summarize the antibiotics recommended for neonatal sepsis and the importance of having them available for urgent administration once a patient is identified
- Describe the pathophysiology of ductal dependent congenital heart disease and the need for immediate administration of alprostadil
- Discuss the recommendations for zidovudine therapy in neonates born with maternal HIV exposure

## Patient case

SB is a 3 day old female presenting to the emergency room with "lethargy and slow breathing". The delivery was without complications and after a 40 hour hospital stay, the neonate and the mother were discharged home. After the first night at home, the mother noted increased sleepiness and disinterest in feeding. Once the slow breathing was noted, the family contacted the pediatrician and was told to immediately bring the baby to the emergency room.

## Neonatal and Pediatric Sepsis

## Neonatal sepsis patient presentation

Which are symptoms of neonatal sepsis?

- A. lethargy
- B. hypothermia
- C. seizures
- D. all of the above



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## Neonatal sepsis patient presentation

- Hyper/hypothermia
- Brady/tachycardia
- Grunting
- Apnea
- Cyanosis
- Lethargy
- Irritability
- Anorexia
- Vomiting
- Jaundice
- Abdominal distension
- Diarrhea
- Absence of meningitis specific symptoms\*

American Academy of Pediatrics. Serious Bacterial Infections Caused by Enterobacteriaceae (With Emphasis on Septicemia and Meningitis in Neonates). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. Accessed August 6, 2018.



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## Neonatal sepsis pathogens

The most common neonatal sepsis pathogens are

- A. *S. pneumoniae* and *N. meningitidis*
- B. Group B Streptococcus, *E. coli*, *L. monocytogenes*
- C. *S. aureus* and *P. aeruginosa*
- D. Cryptococcus and Fusarium



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## Neonatal sepsis pathogens

- Group B streptococcus
  - *Streptococcus agalactiae*
  - Primary gram positive pathogen
  - Maternal testing prior to delivery
  - Prophylactic antibiotics for mother do not completely rule out acquisition
- *Escherichia Coli*
  - Major gram negative pathogen for neonatal sepsis
  - Higher risk in patients with maternal chorioamnionitis, low birth weight, birth prior to 37 weeks gestation, and prolong rupture of membranes

American Academy of Pediatrics. Group B Streptococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. Accessed August 6, 2018.



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## Neonatal sepsis pathogens

- *Listeria monocytogenes*
  - Primarily a foodborne transmission to the mother
    - Ready to eat lunch meat and hot dogs
    - Products made from unpasteurized milk
    - Sprouts
  - Gram positive rod, facultative anaerobe
  - Still considered a pathogen but “common” perhaps not

Muchler et al. Epidemiology of Bacteremia in Downborn Healthy Preterm Infants: A Follow-up Study. Hospital Pediatrics. 2015;5(5):292-304.

American Academy of Pediatrics. Serious Bacterial Infections Caused by Enterobacteriaceae (With Emphasis on Septicemia and Meningitis in Neonates). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book, 2018 Report of the Committee on Infectious Diseases. 33rd ed. Itasca, IL: American Academy of Pediatrics; 2018. Accessed August 5, 2018.

## Early onset sepsis vs. late onset sepsis

### Early onset sepsis

- Less than 72 hours from birth
- More likely to be associated with pathogens from the birth canal

### Late onset sepsis

- More than 72 hours from birth
- Extends through 8-12 weeks of age
- May still include birth canal pathogens
- Increased risk of *S. pneumoniae*, *S. aureus*
- Commonly associated with line infection, prolonged hospitalization

## Empiric antibiotic regimen

What would be an appropriate empiric antibiotic regimen for this patient?

- ceftriaxone
- ampicillin and cefotaxime
- vancomycin and cefepime
- ampicillin and gentamicin
- B and D

## Neonatal concerns with ceftriaxone

- Does not cover *L. monocytogenes*
- Displaces bilirubin from plasma protein
  - Increased risk of hyperbilirubinemia
  - Increased risk of gall bladder disorders
- Chelates with ionized calcium in soft tissues
  - Deposits stone in kidneys and lungs
  - Can result in organ dysfunction and death

Bradley et al. Intravenous Ceftriaxone and Calcium in the Neonate: Assessing the Risk for Cardiopulmonary Adverse Events. Pediatrics. 2009;123:e609-e613

## Empiric Antibiotic Regimen

- Ampicillin & gentamicin
  - Covers major early onset neonatal sepsis pathogens
  - Be aware of your antibiogram – does gentamicin cover E. coli in your area?
  - Does require therapeutic drug monitoring (TDM) if continued beyond 48 hours
  - Has reasonable CNS penetration due to a immature blood brain barrier
- Ampicillin & cefotaxime
  - Covers major early onset neonatal sepsis pathogens
  - More consistent coverage against E. coli
  - Better supportive data for CNS penetration

American Academy of Pediatrics. Group B Streptococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SL, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 71st ed. Itasca, IL: American Academy of Pediatrics; 2018. Accessed August 6, 2018.

American Academy of Pediatrics. Serious Bacterial Infections Caused by Enterobacteriaceae (With Emphasis on Septicemia and Meningitis in Neonates). In: Kimberlin DW, Brady MT, Jackson MA, Long SL, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 71st ed. Itasca, IL: American Academy of Pediatrics; 2018. Accessed August 6, 2018.

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## Drug shortages – of course!

### Cefotaxime – on ASHP shortage list since 2013

- Hospira stopped making cefotaxime
- Baxter stopped making cefotaxime
- Sanofi-Aventis stopped making cefotaxime
- Hikma Pharmaceutical (West Ward) – has raw material and demand issues
  - Long term back order
  - No release date

Wheeler, M. July 5<sup>th</sup>, 2018. Cefotaxime sodium injection. ASHP Current Drug Shortages. Accessed from [www.ashp.org/drug-shortages](http://www.ashp.org/drug-shortages)

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## Substitutions for neonatal sepsis

- American Academy of Pediatrics Recommendation
  - Use ceftazidime in place of cefotaxime
- When can we use ceftriaxone safely
  - Patients over 28 days of age

Alternatives to consider during cefotaxime shortage. AAP News Feb 2015, E150225-1

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## Survey

### In your facility

- Ampicillin and ceftazidime/cefotaxime are compounded and sent by pharmacy 24/7
- Ampicillin and ceftazidime/cefotaxime are available in Pyxis and compounded by nursing staff
- Ampicillin and ceftazidime/cefotaxime are available in an after hours cabinet / room and compounded by nursing staff
- Ampicillin or cefotaxime/ceftazidime are not stocked in an accessible place for urgent/emergent use

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## Recommendations for Pediatric Sepsis

- No national guidelines
- Institution specific recommendations
- Usually related to a primary disease state
  - Pneumonia
  - Meningitis – with symptoms
  - UTI
  - Abdominal infection
- Integrate local antibiogram data into empiric therapy choices



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## Outside Support / Forcing Functions

### Gabby's Law

- In effect in August 2016
- Requires hospitals to:
  - Implement an evidence-based process for quickly recognizing and treating adults and children with sepsis
  - Train hospital staff to identify and treat patients with possible sepsis
  - Collect sepsis data to improve care and provide it to the state



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## Outside Support / Forcing Functions

### IDPH

- Suggest pediatric sepsis quality indicators
  - Sepsis screening protocols, triggers, order sets
  - IV access and fluid bolus within 20 minutes of recognition of sepsis
  - Antibiotic administration within first hour (or defined timeframe per institution)



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## A new wrinkle to our case...

SB is admitted for spinal tap and antibiotics. As the baby was being prepped for the spinal tap, the baby developed tachycardia and hypotension. Cyanosis was noted by the medical team.



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## Emergent Presentation of Congenital Heart Disease

## Fetal Circulation

- Blood is oxygenated by the placenta
- Lungs are bypassed when in utero
- After birth, ductus arteriosus and foramen ovale close
  - Changing pressures
  - Exposure to oxygen
  - Decreased exposure to prostaglandins

## Congenital Heart Disease (CHD)

- 60-70% of patients have diagnosed CHD prior to delivery
- Leading cause of birth defect-associated illness and death in infants
- Risk of heart defects increased with early-onset (< 34 weeks) preeclampsia, preeclampsia with growth restriction, and severe preeclampsia
- Associated with multiple genetic disorders

Lands, B et al (2013) Prenatal Diagnosis of Congenital Heart Disease and Birth Outcomes. *Pediatric Cardiology*, 34(3), 597-605.

Auger N et al. Association Between Preeclampsia and Congenital Heart Defects. *JAMA*. 2015 Oct 20;314(15):1588-98

8. ELEVATE Prevalence of congenital heart disease. *Curr Cardiol Rev*. 2010 May;6(2):95-7.

## Congenital Heart Disease

### Cyanotic Heart Lesions

- Tricuspid/Pulmonary Atresia (DD)
- Transposition of the Great Vessels (DD)
- Tetralogy of Fallot (DD\*)
- Total Anomalous Pulmonary Return (DD)
- Hypoplastic Left Heart Syndrome (DD)
- Truncus Arteriosus

### Non-cyanotic Heart Lesions

- Atrial Septal Defect
- Ventricular Septal Defect
- Pulmonary Stenosis (DD\*)
- Coarctation of the Aorta (DD\*)
- Patent Ductus Arteriosus

DD = ductal dependent

DD\* = ductal dependent physiology based

## Treatment

- Stabilization and referral
- Prostaglandins to keep the ductus arteriosus open
- Alprostadil – prostaglandin E<sub>1</sub>
  - 0.05 – 0.1 mcg/kg/min by continuous infusion
    - Titrate to effect doses of 0.01-0.4 mcg/kg/min reported
  - Common side effects – apnea, hypotension
  - Prepare to a concentration of 10mcg/ml (per VON, ISMP)
  - Refrigerated, comes as a 500mcg/ml ampule
  - NIOSH list
  - Intermittent shortages / back order



## Survey

- A. My facility stocks alprostadil and I know where to find it
- B. My facility stocks alprostadil and I don't know where to find it
- C. My facility does not stock alprostadil
- D. I'm not sure if my facility stocks this



## Survey

- A. My facility has a standard dilution / order set in which to order alprostadil drips if necessary
- B. My facility does not have a standard dilution / order set in which to order alprostadil drips if necessary
- C. I don't know



## Alprostadil acquisition ideas

- \$700 for a box of 5 ampules
- Use system resources – split a box
- Confirm that any transport is bringing drug to the site



## Maternal HIV Transmission

## Patient Case

A woman presents to the emergency room in advanced stages of labor. She has not had any prenatal care. The rapid HIV test comes back positive and it apparent that she is going to deliver prior to transfer to the tertiary referral center.

## Intrapartum Management

- If there's time...
- Intravenous zidovudine
  - Should be administered to women with HIV RNA >1,000 copies/mL or unknown HIV RNA
  - May be considered in women with HIV RNA between 50 and 99 copies/mL
  - Dose: 2mg/kg/load, 1mg/kg/hour continuous infusion until cord clamp

## Two sets of guidelines for neonatal therapy

- Department of Health and Human Services
  - [aidsinfo.nih.gov](http://aidsinfo.nih.gov)
- Illinois Perinatal HIV Hotline
  - 800-439-4079
- Either set of guidelines can be used

## Risk levels regarding perinatal transmission – HHS Guidelines

### High Risk

- Mothers who received neither antepartum nor intrapartum ARV drugs
- Mothers who received only intrapartum ARV drugs
- Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal
- Mothers with acute or primary HIV infection during pregnancy or breastfeeding

### Low Risk

- Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at <http://www.hivguidelines.org/content/hivguidelines/perinatal.pdf>. Accessed August 16<sup>th</sup>, 2018.

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## Neonatal Treatment Guidelines – HHS Guidelines

### • High Risk

- 6 weeks of therapy
- Two options
  - Zidovudine – 4mg/kg/dose PO BID
  - Nevirapine x 3 doses
    - 12mg (not weight based)
    - 2 doses 48 hours apart, one dose 96 hours after second dose

Or

- 3 drug regimen
  - Zidovudine 4mg/kg/dose PO BID
  - Lamivudine 2mg/kg/dose PO BID
  - Nevirapine 6mg/kg/dose PO BID

### • Low Risk

- 4 weeks of therapy
- Zidovudine 4mg/kg/dose PO BID

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at <http://www.hivguidelines.org/content/hivguidelines/perinatal.pdf>. Accessed August 16<sup>th</sup>, 2018.

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## Risk levels regarding perinatal transmission – Illinois Perinatal HIV Hotline

### High risk

- Infants born < 33 weeks gestation
- Infants born to women whose HIV viral load was detectable (anything greater than 20 copies/mL) after 28 0/7 weeks gestation
- Infants born to women who did not receive antepartum antiretroviral therapy
- Infants born to women who started antiretroviral therapy after 13 0/7 weeks gestation
- Infants born to women who became infected with HIV or seroconverted during pregnancy
- Infants born to women diagnosed with HIV during labor or postpartum

### Low risk

- All other infants

Hotline Best Practices for Care of Infants with Perinatal Exposure to HIV. (April 2017). Retrieved from <http://www.hivperinatalhotline.org/content/resources/hotline-best-practices-for-care-of-infants-perinatal-exposure-hiv>.

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## Neonatal Treatment Guidelines – Illinois Perinatal HIV Hotline

### High Risk

- Zidovudine 4mg/kg/dose PO BID x 6 weeks
- Lamivudine 2mg/kg/dose PO BID – duration dependent on neonatal HIV PCR results
- Nevirapine 6mg/kg/dose PO BID – duration dependent on neonatal HIV PCR results

### Low Risk

- 4 weeks therapy
  - Goal of zidovudine administration in the first hour after delivery
  - 4mg/kg/dose PO BID
- Or
- 2-2.9ml – 1ml PO BID
  - 3-3.9ml – 1.5ml PO BID
  - 4-4.9ml – 2ml PO BID

Hotline Best Practices for Care of Infants with Perinatal Exposure to HIV. (April 2017). Retrieved from <http://www.hivperinatalhotline.org/content/resources/hotline-best-practices-for-care-of-infants-perinatal-exposure-hiv>.

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## What to keep and how much?

- Zidovudine for injection - \$35 / vial (\$350 for 10 pack)
- Zidovudine for oral solution - \$80 / bottle
- Lamivudine (Epivir) - \$120 / bottle
- Nevirapine (Viramune) - \$223 / bottle



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## What is the best perinatal treatment for the neonate in our patient case?

- No therapy needed
- Zidovudine 4mg/kg/dose PO BID x 4 weeks
- Zidovudine 4mg/kg/dose PO BID x 6 weeks
- Zidovudine 4mg/kg/dose PO BID x 6 weeks, plus lamivudine and nevirapine



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## Survey

- My institution has a clinical guideline or order set available for neonatal HIV prophylaxis and has all medications available
- My institution has a clinical guidelines or order set available for neonatal HIV prophylaxis and does not have all medications available
- My institution does not have a clinical guideline or order set for neonatal HIV prophylaxis



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## Caring for pediatric patients

- Individualized pediatric doses
- Manipulation of commercially available products
- More likely to be on the receiving end of a dosing error
- Newly available pediatric dosage forms retain brand



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## Training to care for pediatric patients

- Competencies for pharmacists and nurses that may care for pediatric patients
- Simulation and drill emergent/urgent situations
- Orientation on where urgently needed and not often used products are stored



## Questions?



## Technology Pearls 2018

Katherine Gauen, Pharm.D.  
 Sarah Seward, Pharm.D., BCPS  
 Sarah Shimosono, Pharm.D.  
 Joshua Schmees, Pharm.D.



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## Controlled Substance Operational Dashboard Pearls

Katie Gauen, PharmD  
 Medication Safety & Compliance Pharmacist  
 Northwestern Memorial Hospital  
[kgauen@nm.org](mailto:kgauen@nm.org)

The speaker has no conflicts of interest to disclose.



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## Learning Objectives – Pharmacists and Technicians

1. Describe the difference between a discrepancy and an exception as related to controlled substance inventory management.
2. List three examples of measures which can help detect and minimize drug diversion, and how to generate reports and analytics to assess the measures.



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## Definitions

- **Discrepancy:** there is a difference between what the ADC *thinks* is in the ADC, and what is *actually* in the ADC
- **Exception:** there is a difference between what an ADC *thinks* it should receive, and what it *actually* receives



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Can you have both an exception and a discrepancy?

CPhT#1 pulls 10 lorazepam tabs for ADC restock out of CSM

CPhT#2 accidentally only puts 5 lorazepam tabs into ADC but does not change quantity when loading (defaulted to expected 10 tabs)

RN accesses lorazepam tabs and does countback

This creates an exception of "**5 short**" because the ADC is "expecting" 10 tabs

This creates a discrepancy of "**- 5**" because the ADC "thinks" there are 10 but there are only 5 tabs

## Other controlled substance reporting features

### Discrepancy resolution reporting

- **Ideally**, discrepancies should be resolved immediately
- **In practice**, policy is to resolve discrepancies by end of shift
- **In reality**, there are times it takes longer than one shift to resolve a discrepancy
- Reporting can help you identify certain pharmacies or ADC locations where discrepancies are NOT resolved in a timely manner, as well as areas where discrepancies are resolved inappropriately

### Override report

- Overrides occasionally must occur for patient needs
- Medications on override depend on hospital policy, care area, etc.
- When necessary to pull drugs on override, follow up should include:
  - Linking override to written order
  - Documenting administration, return, or waste of product
- Reporting can help identify areas where one or more of the follow up steps are not completed appropriately

### ADS Overrides

#### Description

This report helps track the workload of automated dispensing stations (ADS). It shows details about medications pulled on override from those ADS machines. The report displays the total number of unlinked, unadministered, and returned orders for each location and each level of grouping.

The report can be grouped by hour, medication, pharmacy, user, or DEA (Controlled Substance) Classification.

#### Report Filter Criteria

Start Date: [REDACTED]

End Date: [REDACTED]

Location(s): NMH NORTHWESTERN MEMORIAL HOSPITAL

Pharmacy: NMH OLSDT OMNI, NMH ARKES 19 TRANSPLANT CLINIC OMNI, NMH FEIN 1 ED EAST OMNI, NMH FEIN 1 ED MIDDLE ...

Medication DEA Class(es): C-II High abuse potential, C-III Moderate dependence, C-IV Limited Dependence, C-V Limited abuse pot...

Grouped by: Pharmacy

[Link to Detail Report](#)

Location	Total Override Pulls	Unlinked Orders	Unadministered Orders	Returned Orders
NMH NORTHWESTERN MEMORIAL HOSPITAL	734	552	523	29
Pharmacy				
NMH FEIN 1 ED EAST OMNI	48	16	13	4
NMH FEIN 1 ED MIDDLE OMNI	23	6	4	1
NMH FEIN 1 ED TRAUMA OMNI	1	0	0	0
NMH FEIN 12E S OMNI	3	3	2	0
NMH FEIN 12W S OMNI	1	0	0	0
NMH FEIN 13E N OMNI	1	1	0	0

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### Null transaction report

- Null transaction = accessing a medication bin without an action (issue, return, cycle count, etc.)
- Impact of subsequent transactions could be negative
- Reporting can be done to look at users who have the most null transactions, and can guide re-education on best practices

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### Match the example with the correct term:

- 1 = exception, 2 = discrepancy
- 1 = discrepancy, 2 = exception
- Both discrepancies
- Both exceptions

#### Example 1

A nurse pulls 2 tramadol tablets out of an ADC when he only electronically documented he was pulling 1 tablet. The next nurse that pulls tramadol and does a countback of the bin will cause a(n) \_\_\_\_\_.

#### Example 2

The pharmacy sends 10 vials of lorazepam to an ADC with a pharmacy technician for restock. One of the vials rolls out of the delivery bag and when the technician restocks the ADC they only document adding 9 vials. This will cause a(n) \_\_\_\_\_.

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### Which of the following reports can be used to follow up on suspected diversion?

- Discrepancy report
- Exception report
- Override report
- All of the above

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# A Dual System Solution to Inventory Optimization

**Sarah Seward, PharmD, BCPS**  
Pharmacy Informaticist  
Hospital Sisters Health System  
Springfield, IL

The speaker has no actual or potential conflicts of interest in relation to this presentation

## Learning Objectives - Pharmacist and Technician

1. Describe the process of concurrently implementing a new carousel inventory management system, along with an automated unit dose packaging system in a new hospital inpatient pharmacy.
2. Discuss the cost savings associated with the implementation of this project.

## Background

- Simultaneous hospital move and EMR conversion
  - Inventory management improvement opportunity
    - Carousel
    - Inventory management software
  - High-speed packager
  - Automated dispensing cabinet coordination
- Decreasing size of department



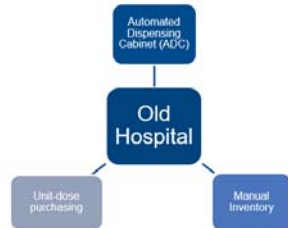
## Primary Objective

- What technologies can we use to function in our reduced department space?
  - How can we maintain inventory with less space?

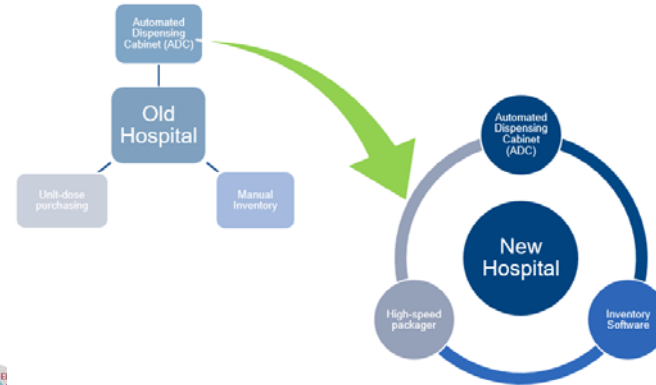
Carousel	Current	One Time	Monthly	Notes
2 Carousels plus additional software	NA	(\$63,344)	(\$7,049)	
Decrease square footage of pharmacy drug storage space needed by 1/3 (\$700/sf to build, \$3.23/sf utilities, \$5.04/sf for maintenance) <sup>1</sup>	NA	\$466,900	\$5,516	Decrease pharmacy drug storage square footage by 1/3 (2000 sq ft to 1333 sqft = 667 sq ft reduced)
<b>Total Cost Savings</b>		<b>\$403,556</b>	<b>(\$1,533)</b>	

<sup>1</sup> Benchmarking 2.0 Health Care Facility Management Report- Speaking their language. <http://www.hfmmagazine.com/articles/394-speaking-their-language>. Last accessed 7/20/16

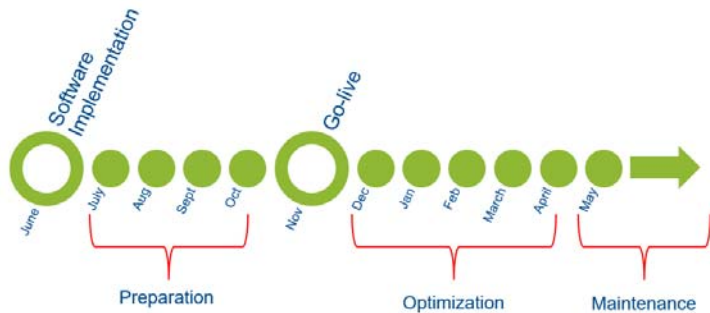
## Project Purpose



## Project Purpose

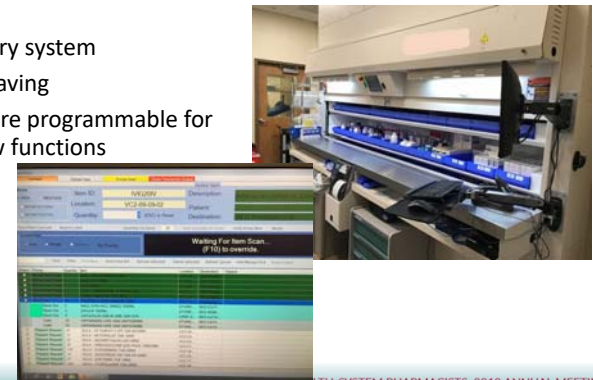


## Timeline



## Inventory Management System

- Carousel inventory system
- Space and cost saving
- Inventory software programmable for desired workflow functions



## High-Speed Packager

- 3 modes of packaging: canister, free-pour, unit dose tray
- One way communication with carousel inventory system
  - Min and max levels in carousel can create queue in packager
  - Low canister quantity can not trigger action in carousel to "refill canister"

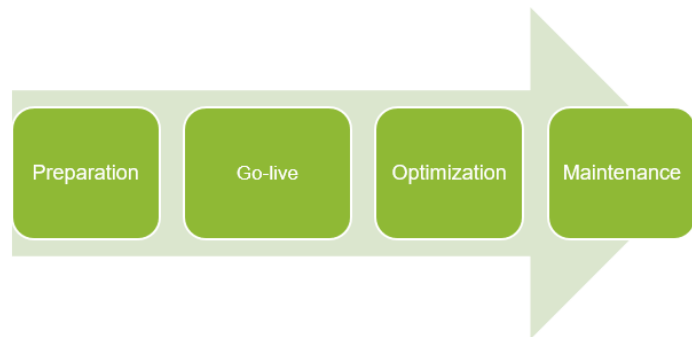


## Automated Dispensing Cabinets

- Two way interface with EMR
- Communicates with carousel to drive technician workflow
- Expanded patient care areas with new hospital
  - Conversion of old cabinets
  - Addition of new cabinets



## Methods



## Preparation

- Organization & randomization of 2 carousels
  - Carousel 1: Unit dose tablets and liquids + common premix IVs
  - Carousel 2: Bulk bottles + IV room medication
- Coordination of inventory revolved around:
  - Type: Bulk bottles (liquids and tablets), unit dose, premix IV solutions, IV room medications
  - Physical: Weight and height (tall shelves)
  - Safety: look alike sound alike, strength
- Order of first set of packager canisters



## Go-live

- New EMR conversion & hospital move
- Physical move of inventory to 2 carousels
- Validation of ~100 packaging canisters
- Move 48 old ADCs to new facility
- Add 9 new ADCs at new facility



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## Optimization

- Needed a better solution to managing inventory
- Carousel:
  - Adjustment of min and max unit dose levels
- ADCs:
  - Evaluation of vend/refill ratio
  - Stock out %
- Packager:
  - Analyze monthly cabinet pulls
  - Order second set of canisters



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## Maintenance

- Ongoing coordination with pharmacy buyer
  - Heavy resident work at project implementation
  - Independent maintenance work by pharmacy buyer
- Carousel & ADCs:
  - Automatically generate reports
  - Create scorecards
- Packager:
  - Third canister order + recycle canisters



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## Results



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## Maximizing Carousel

- Fine tune minimum and maximum levels on unit dose
  - Drive bulk inventory management

	Min	Max
Slow: ≤ 49 meds	3 days	7 days
Medium: 50-199 meds	5 days	10 days
Fast: ≥ 200 meds	7 days	14 days

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
1. Row Labels	Sum of Quantities	Sum of Average quantity	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply	Sum of 3 day supply
2. ACTOFASTAB	2533	91	182	243	406	568	109	230	237	750	75															
3. ADAPRODOL	1507	49	97	146	263	340	184	330	631	788	7															
4. GABAPROCAP	1111	36	70	109	182	235	109	139	200	433	74															
5. VIOXX	854	28	55	83	138	181	50	100	130	340	56															
6. ACTOFASTAB	737	23	46	69	109	142	104	79	120	375	7															
7. PRECISETAB	659	21	42	64	109	149	51	79	120	375	7															
8. GABAPROCAP	406	13	26	39	68	92	30	40	120	240	7															
9. GABAPROCAP	374	12	24	36	60	84	30	40	120	240	7															
10. ADAPRODOL	349	12	24	36	60	84	30	40	120	240	7															
11. THEOPHYLLINE	324	10	20	30	50	70	20	30	120	120	7															
12. TOPROL-XL	262	8	17	25	42	58	30	40	120	120	7															
13. FLOANIDIN	232	7	14	21	36	49	30	40	120	120	7															
14. FLOANIDIN	232	7	14	21	36	49	30	40	120	120	7															
15. ADAPRODOL	197	6	12	18	30	40	30	40	120	120	7															

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## Cost Savings for Packager

- Estimated monthly savings = \$6,017.95
  - Added 105 additional new medications
- Increase in technician time likely offset by overall savings

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## Cost Analysis Factors

	Pre Nov	Post Nov
Carousel	\$749,887.13	\$914,137.79
ADCs	\$5,785.66/machine	\$5,547.63/machine
High-speed packager	\$11,653.54	\$5,635.59
Average daily census	198	221
Inventory per patient	\$5,189.89	\$5,567.21

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## Scorecard – Carousel Inventory

Carousel Inventory											
Activity Scorecard											
Monthly Cost (Q1H18)	Cost On Hand	# of meds	# of items	Cost above Max	In Potential Savings	Max Potential Savings					
\$ 1,398,758.10	\$ 1,398,758.10	1,049	84,882	\$ 557,781.17	\$ 811,758.93	\$ 406,433.11					
Breakdown by Cost Level											
Monthly Cost	Cost On Hand	Min Cost Savings	Max Cost Savings	Monthly Cost	Cost On Hand	Min Cost Savings	Max Cost Savings				
Low	\$ 233,374.33	\$ 87,593.76	\$ 21,043.81	\$ 54,646.18	Low	\$ 1,284,417.18	\$ 1,005,788.45	\$ 18,581.36	\$ 252,727.44		
Medium	\$ 233,782.48	\$ 88,383.82	\$ 12,374.81	\$ 33,232.22	Medium	\$ 181,742.39	\$ 244,478.42	\$ 38,894.42	\$ 14,857.27		
High	\$ 1,931,601.29	\$ 1,020,781.59	\$ 141,341.57	\$ 290,604.99	High	\$ 222,805.29	\$ 64,121.37	\$ 7,224.31	\$ 141.10		
Top 10 Min Cost Savings											
Medication	Cost Savings	Current Max	Goal Max								
ALTEPLASE 100MG VIAL	\$ 48,227.63	5	0.3								
VELOCARD 250 MG VIAL	\$ 16,243.53	3	0.5								
INFUSION 100MG	\$ 12,387.29	20	0.7								
PAPAPAZO 100 MG	\$ 8,447.62	80	2.8								
DOXYFENILIN 100 MG VIAL	\$ 3,963.25	5	0.7								
DOXYFENILIN 100 MG VIAL	\$ 3,837.86	3	0.5								
DOXYFENILIN 100 MG VIAL	\$ 2,874.73	25	1.4								
DOXYFENILIN 100 MG VIAL	\$ 2,868.82	20	1.3								
DOXYFENILIN 100 MG VIAL	\$ 2,777.62	15	0.5								
DOXYFENILIN 100 MG VIAL	\$ 2,777.77	20	1.2								
SULGAMIN 100MG INJECTION 5ML	\$ 2,723.73	20	1.8								
Top 10 Qty Above Max											
Medication	Qty Above	Cost									
DOXYFENILIN 100 MG VIAL	2,823	\$ 3,872.31									
DOXYFENILIN 100 MG VIAL	2,787	\$ 3,888.72									
DOXYFENILIN 100 MG VIAL	1,785	\$ 2,726.88									
DOXYFENILIN 100 MG VIAL	1,881	\$ 749.89									
DOXYFENILIN 100 MG VIAL	1,841	\$ 1,065.89									
DOXYFENILIN 100 MG VIAL	1,841	\$ 48.49									
DOXYFENILIN 100 MG VIAL	831	\$ 541.48									
DOXYFENILIN 100 MG VIAL	687	\$ 416.77									
DOXYFENILIN 100 MG VIAL	681	\$ 38.88									

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# Scorecard – Medication Dispensing Unit Inventory

# Conclusion

- Automation can help streamline operations
- Coordinating a carousel, high-speed packager and dispensing cabinets can provide significant cost and space saving benefits

```
graph TD; ADC((Automated Dispensing Cabinet (ADC))) --- CH((New Hospital)); HSP((High-speed packager)) --- CH; IS((Inventory Software)) --- CH;
```

The diagram illustrates a central hub-and-spoke model for a new hospital. At the center is a dark blue circle labeled "New Hospital". Surrounding this central hub are three smaller, light blue circles, each representing a different automated system: "Automated Dispensing Cabinet (ADC)" at the top, "High-speed packager" at the bottom left, and "Inventory Software" at the bottom right. These three peripheral circles are connected to the central hub by a thick, light blue circular line, indicating a seamless integration and data flow between all components.

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# Contributors

- Josh Schmees, PharmD – Pharmacy Informaticist
- Emily Pettit, PharmD – PGY1 Resident
- Barb Fiore, CPhT – Pharmacy Support Services Coordinator

- # Which of the following is a benefit of implementing a carousel storage system?
- A. Takes up a lot of physical storage space
  - B. Streamlines inventory management
  - C. Makes the pharmacy 340B compliant
  - D. Interfaces with only one electronic medical record system



Combining a high-speed packager with a carousel storage system can provide which of the following benefits?

- A. A cost saving opportunity
- B. Decreased efficiency of pharmacy personnel workflow
- C. A process that is totally dependent on pharmacist supervision
- D. Hinders coordination of automated dispensing cabinet medication replenishment



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## IV Room Workflow System: Pros and Cons

Reina Shimozone, PharmD  
PGY2 Pharmacy Informatics Resident  
Hospital Sisters Health System  
O'Fallon, Illinois



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## Contributors

- Joshua Schmees, PharmD
- Sarah Seward, PharmD, BCPS

Disclosure: This speaker and the contributors have no actual or potential conflicts of interest in relation to this presentation.



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## Hospital Sisters Health System

- 15 hospitals spanning both IL and WI
- PGY2 Pharmacy Informatics program based out of St. Elizabeth's hospital



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## Learning Objective – Pharmacist and Technician

- Describe the pros and cons on using IV room workflow software



## Background

- Institute of Safe Medication Practices (ISMP) report
  - 9% error rate in sterile products
  - Majority incorrect dose/strength

Safety Gaps in IV Workflow
Syringe pull-back method
Calculations
Product Selection
Error detections

Institute for Safe Medication Practices Sterile Preparation Compounding Safety Summit DRAFT OF THE PROCEEDINGS—Aug. 2012



## Background

- ISMP Targeted Medication Safety Best Practices for Hospitals
  - Technology to assist in verification of compounded sterile products
  - Recommend barcode scanning
  - Workflow software should be used to augment manual processes



Proposed Revisions to the ISMP Guidelines for SAFE Preparations of Sterile Compounds, ISMP, 2016.



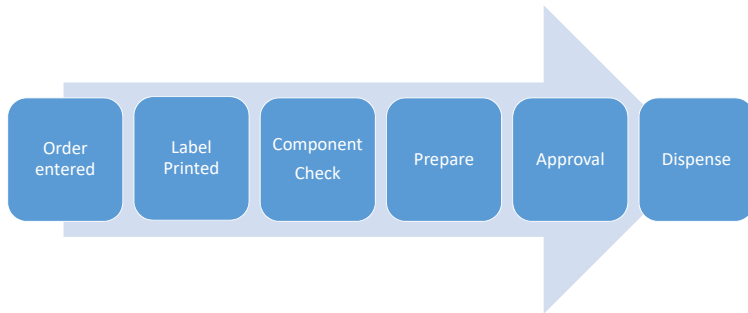
## IV Workflow Systems

- Systems comprised of technologies that help with manual processes for preparing and verifying compounded products
- Examples:
  - Barcode scanning
  - Digital image capturing
  - Gravimetric verification
  - IV Robotics

ISMP Sterile Preparation Compounding Safety Summit: Guidelines for Safe Preparation of Compounded Sterile Preparations ISMP, 2013.



## IV Workflow Systems



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## Advantages of IV Workflow Systems

- Improved Safety
  - Automated dose calculations
  - Eliminating pull back method
  - Barcode scanning
  - Remote approval
- Historical Documentation
- Optimize/customize workflow

Safety Gaps in IV Workflow	Advantages
Syringe pull-back method	Image capturing
Calculations	Calculated in System
Product Selection	Barcode Scanning
Error detections	Automated tracking

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## Barriers to IV Workflow Systems

- Time
- Increased informatics support
  - Inability to scan barcode
  - Technological troubleshooting
- Training
- Cost

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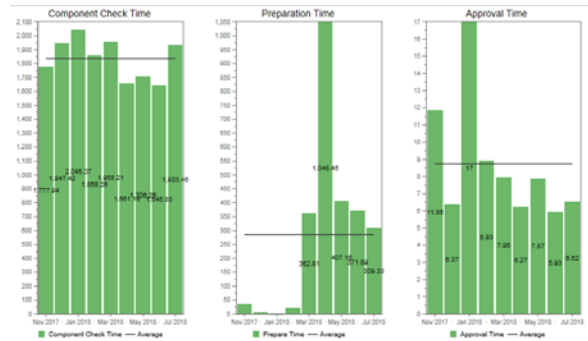
## Institutional Overview

- Average: 220 - 280 IVs/day
- Bed size: 144 beds
- Live in November 2017
  - New hospital/EHR/workflow
  - 2 iPads
- Hazardous/Chemo room
- IV room

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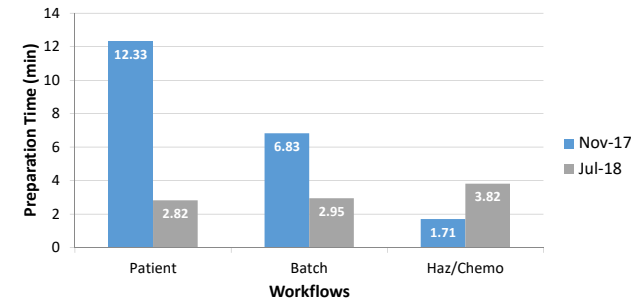
## Reports



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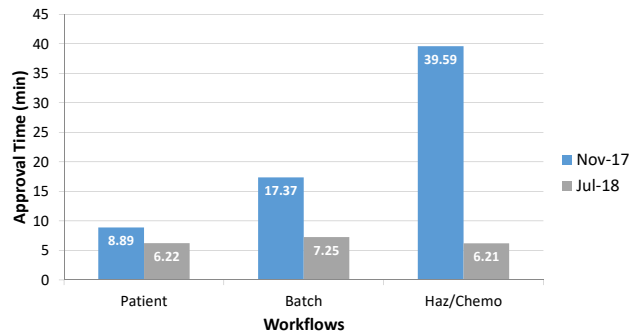
## Reports: Preparation time



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## Reports: Approval Time



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## Reports

Reject Reason	November 2017	July 2018
Unspecified/Other	5	-
Wrong Dose/Volume	3	-
See Notes/Pharmacist	2	1
Missing Component Information	1	-
Missing Image	1	-

	November 2017	July 2018
Reject Rate	1.34%	0.05%
Error Rate	14.04%	3.2%
Total Compounded	890	1883

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## Reports

### November 2017

Top 5 Wrong Scanned Component	Number of Wrong Scans
Meropenem 1g Powder for solution for injection	42
Oxacillin Sodium 2g Powder for solution for injection	13
SODIUM CHLORIDE 0.9 % IV SOLN 250 ML	9
Cefepime Hydrochloride 2g Powder for solution for injection	9
ACYCLOVIR SODIUM 50 MG/ML IV SOLN	6
<b>Total Wrong Scans</b>	<b>125</b>

### July 2018

Top 5 Wrong Scanned Component	Number of Wrong Scans
SODIUM CHLORIDE 0.9 % IV SOLN 100 ML	13
Oxacillin Sodium 2g Powder for solution for injection	10
EPINEPHRINE 1 MG/ML IJ SOLN	7
VANCOMYCIN HCL 500 MG IV SOLR	4
SODIUM CHLORIDE 0.9 % IV SOLN 500 ML	3
<b>Total Wrong Scans</b>	<b>61</b>

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## Summary

- IV Workflow Systems detect human errors during sterile compounding
  - Barcode scanning can improve wrong product selection
  - Digital images document and detect errors missed by pull-back method
- IV Workflow Systems allows facilities to analyze the workflow

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Which of the following is NOT a benefit of using IV room workflow software?

- Removal of syringe pull-back method
- Remote approval
- Automated dose calculations
- Image capturing
- Reduced time spent

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## Using Forms and Spreadsheets to Expedite Requests and Collect Documentation

Joshua Schmees, PharmD, PGY2 Pharmacy Informaticist  
 Pharmacy Informatics Residency Program Director  
 Hospital Sisters Health System  
 O'Fallon, Illinois

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## Contributors

- Joshua Schmees, PharmD
- Sarah Seward, PharmD, BCPS
- Disclosure: This speaker and contributors have no actual or potential conflict of interest in relation to this presentation

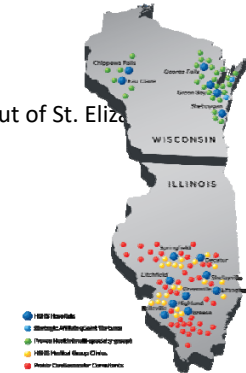


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## Hospital Sisters Health System

- 15 hospitals spanning both IL and WI
- PGY2 Pharmacy Informatics program based out of St. Elizabeth's hospital



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## Learning Objective – Pharmacist and Technician

- Explain how forms can be setup to expedite requests or collect documentation



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## Background

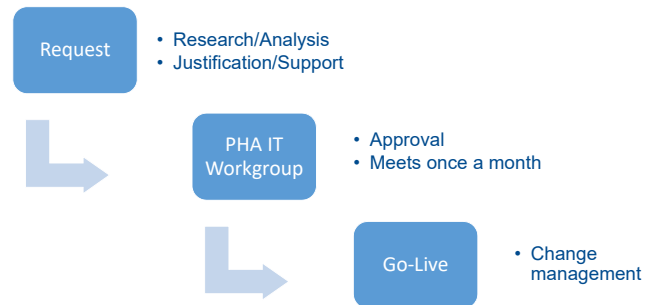
- Over 2017-2018, we began converting hospitals to one single EHR
- From 2011 to present we have had pharmacy IT workgroup  
Comprised of:
  - Pharmacy Informaticists
  - Pharmacy Directors
  - Pharmacy Analysts
  - System pharmacy leaders
  - Evidence Based Medicine Coordinators



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## Request Workflow



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## Problems

- Everyone was moving to single build platform
  - Standardization
- Every request had the same workflow
- Not all requests required intense workup/discussion
- Delay in builder approval

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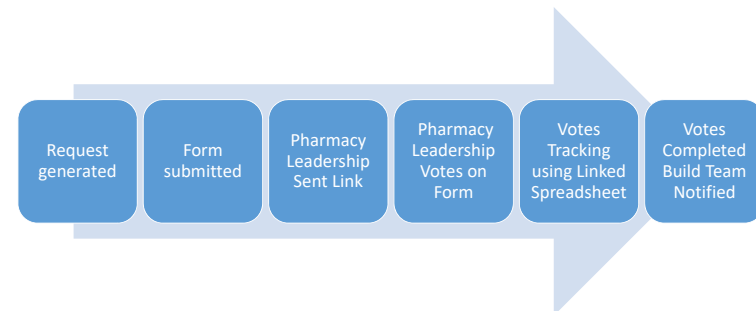
## Solutions

- Create a process that operates outside of monthly meetings
- Create a tool for inputting requests
- Create a tool for collecting votes on requests

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## Expedited Process



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## Workflow Considerations

- Consensus
  - Required 100% consensus
- How to handle discussion needs?
  - Email
  - Move to meeting
  - Direct verbal clarifications
- Minutes inclusion
  - Add approvals to monthly agendas
- Who decides what is expedited?
  - Pharmacy Informatics



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## Input Form



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## Voting Form



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## Google Form Considerations

- Map out your data
  - Easier to sequence in the beginning than the end
- Field presentation Drop-down, List, Check Boxes, Radio Buttons, Free Text
- Required Fields
- Should Drop-Down be synced?



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## Google Form Considerations

- Is there any unique needs of this process?
  - Two different forms for one process
  - Prevent certain responses
  - Consider third party add-ons (eg. email notification for forms, form ranger)
- Do I need to send data to spreadsheet?

## Google Sheets

- Landing place for data for each form

Timestamp	Does this request...	Who is requesting it	SBAR Title	Situation	Background	Assessment	Recommendation
1/20/18 12:20:51 No							
2/14/2018 10:50:48 No			Add due time for irrigation drip rate code - CHG0075215	Shake vial with the vial per instructions	Occasionally in the chart		
2/14/2018 11:02:22 No			Prap instructions for Ambicome IV - CHG0079707	Prap instructions for Ambicome IV - CHG0079707	Prap instructions for Ambicome IV - CHG0079707	Prap instructions for Ambicome IV - CHG0079707	Prap instructions for Ambicome IV - CHG0079707

Timestamp	Site Title	T	Department	Site	Combined	Approval (Signature)	Approval (Date)	Approval (Signature/Date)
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							
6/16/2018 12:43:05	Sperry and French Ave for under 7 years							

## Google Sheets

- Tables for drop-downs

Pharmacy IT SBAR (Responses)				
Director Name				
1	Director Name	Site		
2		SMT		
3		SUS		
4		SFL		
5		FWO		
6		WWD		
7		ISEO		
8		S.I.H.S.I.R.H.F.G.		
9		SAE		
10				

Timestamp	Does this request...	Who is requesting it	SBAR Title
1/20/18 12:20:51 No			
2/14/2018 10:50:48 No			Add due time for irrigation drip rate code - CHG0075215
2/14/2018 11:02:22 No			Prap instructions for Ambicome IV - CHG0079707

## Google Sheets

- Add formulas to adjust data as needed

Filter	Status	Approval Votes	Rejection Votes	Discussion Votes	Total votes
		AREA	AREA	AREA	
entration of 4 mg/mL. Shake vial for 30 seconds. Vent vial to approved	approved	8	0	0	8
	approved	8	0	0	8
	approved	8	0	0	8

## Google Sheet Considerations

- Auto-save automatic and no way to turn off
- Excel formulas and Google Sheet formulas are not always equivalent
  - Pivot tables are possible
- Consider using an array formula to repeat a result for each new form submission
- If syncing a drop down, do you want it auto-removed with a certain condition
  - Use If statement to create blank



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## Results

- 41 expedited requests since February 2018
- 1 rejection
- 5 required additional discussion
- 85.3% approval rate



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## Conclusion

- Google Forms/Sheets can be effective tools
- Creating a process outside of meetings can be impactful
  - More time for review and reduce monthly agenda items



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## Which is NOT a consideration for building a form?

- Review if data should be submitted in drop-down instead of radio button
- Build the form first and adjust as you go
- Create a linked spreadsheet to manipulate and review submitted data
- Consider third party add-ons (eg. Form Ranger, email notification for forms)



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## Acknowledgements

- Pharmacy Informatics Team
  - Michelle Smith, Eric Knox, Sean Howes, and Sarah Seward
- Pharmacy Leadership Team
  - Sue Wheeler, John VanDeVoort, Brandi Strader
  - Brian Strader, Stacey Jones, Rob Runde, Joel Tucker, Julia Schimmelpfennig



## Questions





## House of Cards: The In and Out of the Patient Protection and Affordable Care Act

Joelle Farano, PharmD  
The University of Chicago Medicine  
September 14<sup>th</sup>, 2018

Contributions by Bryan McCarthy, Jr. Pharm.D., MS, BCPS

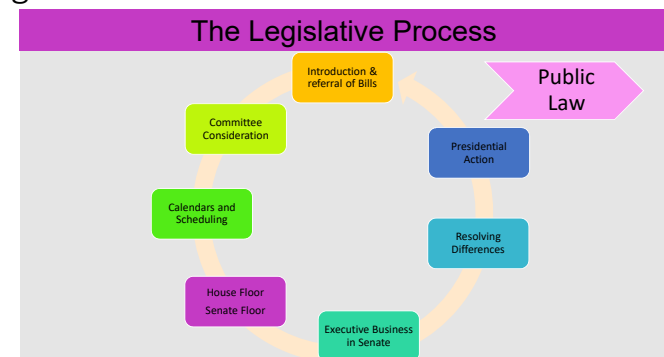
### Disclosure

- I nor contributor have any conflicts of interest to disclose
- Intent – no political party support or endorsement

### Learning Objectives – Pharmacists and Technicians

1. Outline key provisions of the Patient Protection and Affordable Care Act (PPACA)
2. Explain support and criticism for the Patient Protection and Affordable Care Act
3. Explain efforts to date of the Congress to repeal, replace, and reform the PPACA and describe current efforts to revise the law

### Background



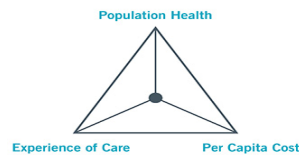
Adapted from The Legislative Process: An Overview. (2018, January 29) Retrieved from: <https://www.congress.gov/legislative-process>

## Triple Aim

Institute for Healthcare Improvement (IHI)

1. Improving the patient experience of care (including quality and satisfaction)
2. Improving the health of populations
3. Reducing the per capita cost of health care

The IHI Triple Aim



Berwick, D. M., Nolan, T. W., & Whittington, J. (2008). The triple aim: care, health, and cost. *Health affairs*, 27(3), 759-769.

## Legislative Background

- Patient Protection and Affordable Care Act (ACA)
- H.R. 3590
  - Patient Protection and Affordable Care Act
  - 111th Congress (2009-2010)
- H.R. 4872
  - Health Care and Education Reconciliation Act of 2010
  - 111th Congress (2009-2010)

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In 111th Congress (Vol. 2010).

Congress, U. S. (2009). HR 4872: Healthcare and education reconciliation act. In 111th Congress (Vol. 2010).

## Key Provisions of the ACA



## Key Provisions of ACA

- Individual Mandate
- Employer requirements
- Public program expansion
- Health insurance exchange
- Insurance expansion
- Financing health reform

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In 111th Congress (Vol. 2010).

## Individual Mandate

- Starting in January 1<sup>st</sup>, 2014, all individuals were required to have health insurance (some exceptions)
- Penalty: \$695 per person (up to a maximum of \$2,085 per family), or 2.5% of household income
- Premium tax credits and subsidies

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).

## Public Program Expansion

- Medicaid expansion
  - State coverage to include all individuals with income up to 133% of the poverty line, including adults without dependent children, beginning January 1<sup>st</sup>, 2014
  - Federal Poverty Line (FPL)

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).

## Public Program Expansion

- Medicaid expansion
  - Supreme Court and Constitutionality

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).

## Public Program Expansion

- Children's Health Insurance Program
  - States to maintain current income eligibility levels for children until 2020

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).

## Health Insurance Exchange

- State options for insurance exchange
  - State set up exchange
  - State and federal government partnership
  - Federal government run exchange
- Benefit tiers- must provide at least 4 levels of coverage
  1. Bronze plan
  2. Silver plan
  3. Gold plan
  4. Platinum plan

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).



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## Health Insurance Exchange

### Ten Essential Health Benefits

- 1) Ambulatory patient services
- 2) Emergency services
- 3) Hospitalization
- 4) Maternity and newborn care (before and after birth) services
- 5) Mental health and substance use disorder services, including behavioral health treatment
- 6) Prescription drugs
- 7) Rehabilitative and ablative services and devices
- 8) Laboratory services
- 9) Preventative and wellness services and chronic disease management
- 10) Pediatric services, including oral and vision care

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).



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## Insurance Expansion

- Adult child may stay on parent's insurance until 26 years of age
- Insurance companies cannot deny for pre-existing condition
- No lifetime limits on coverage

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).



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## Financing Health Reform

- Tax changes
  - Individual mandate, premium tax credits, subsidies
  - Cap on flexible spending
  - Cadillac tax

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In *111th Congress* (Vol. 2010).



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## Financing Health Reform

- Centers for Medicare/Medicaid Services:
  - Center for Medicare and Medicaid Innovation (CMMI) established

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In 111th Congress (Vol. 2010).



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## Financing Health Reform

- Annual fees
  - Pharmaceutical manufacturing: \$2.8-4.1 billion/year
  - Health insurance sector: \$8-14.3 billion/year

Congress, U. S. (2009). HR 3590: Patient Protection and Affordable Care Act. In 111th Congress (Vol. 2010).



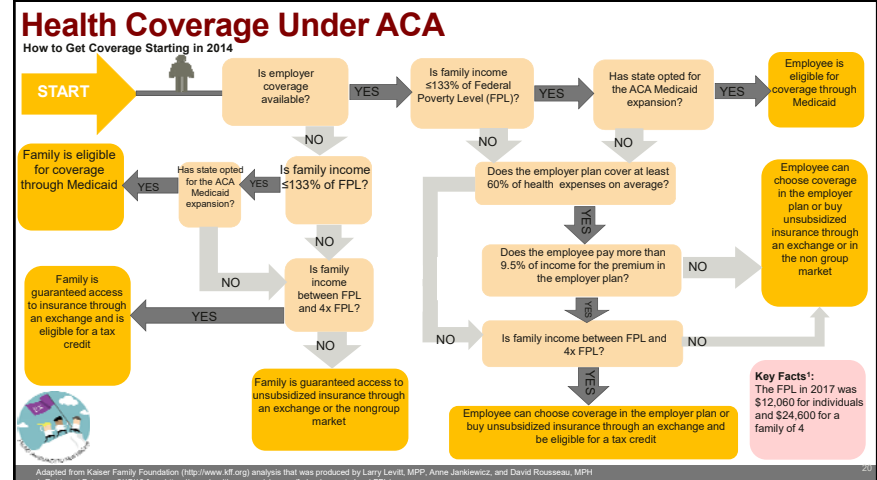
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Which of the following services is NOT one of the ten essential health benefits?

- Ambulatory patient services
- Emergency services
- Maternity and newborn care (before and after birth) services
- Preventative and wellness services and chronic disease management
- Cosmetic surgeries



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## ACA Support and Criticism



## Key Issues Regarding ACA

- Is healthcare is a right or a privilege?
- Society funded healthcare
- Morality of government involvement
- Free market influence of healthcare reforms

Sade, R. M. (2012). The Health Care Reform Law (PPACA): Controversies in Ethics and Policy.

## Democratic Support for ACA

- Nancy Pelosi
  - Minority Leader of House of Representatives
  - Former Speaker of the House



## Democratic Support for ACA

**"We have to pass the bill so that you can find out what is in it —** away from the fog of the controversy. You've heard about the controversies within the bill, the process about the bill, one or the other. But I don't know if you have heard that it is legislation for the future, not just about health care for America, but about a healthier America, where preventive care is not something that you have to pay a deductible for or out of pocket. Prevention, prevention, prevention—it's about diet, not diabetes. It's going to be very, very exciting."

-Nancy Pelosi, National Association of Counties' 2010 legislative conference

## Democratic Claims of ACA

- Expanded coverage
- New consumer protections
- Savings and benefits for seniors
- Savings for other consumers
- Savings for taxpayers
- Improved quality

Health Care. 2018, February 19 Retrieved from <https://pelosi.house.gov/issues/health-care>

## United States Health Care Reform Progress to Date and Next Steps

**Clinical Review & Education**

**JAMA | Special Communication**

**United States Health Care Reform**  
Progress to Date and Next Steps

Barack Obama, MD

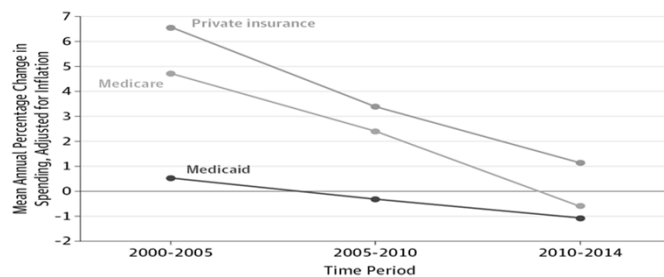
**IMPORTANCE:** The Affordable Care Act is the most important health care legislation enacted in the United States since the creation of Medicare and Medicaid in 1965. The law implemented comprehensive reforms designed to improve the accessibility, affordability, and quality of health care.

**OBJECTIVES:** To review the factors influencing the decision to pursue health reform, summarize evidence on the effects of the law to date, recommend actions that could improve the health care system, and identify general lessons for public policy from the Affordable Care Act.

**Editorials** pages 492, 493, 495, and 497  
**CME Quiz** at [jamanetwork.com](http://jamanetwork.com) and **CME Questions** page 537

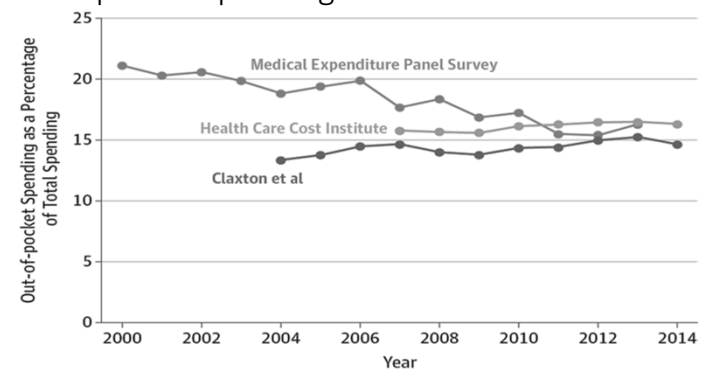
Obama B. United States Health Care Reform Progress to Date and Next Steps. JAMA. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

## Rate of Change in Real per-Enrollee Spending by Payer



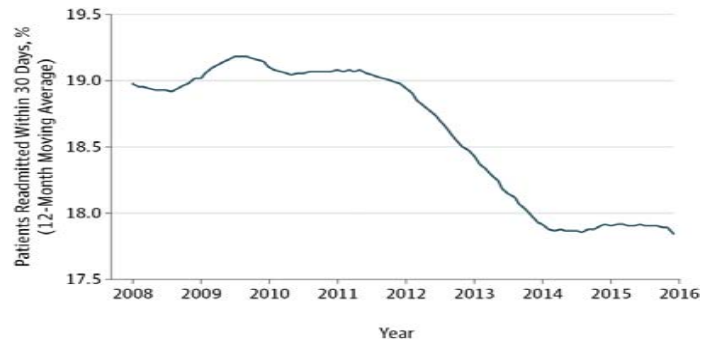
Obama B. United States Health Care Reform Progress to Date and Next Steps. JAMA. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

## Out-of-pocket Spending



Obama B. United States Health Care Reform Progress to Date and Next Steps. JAMA. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

## Readmission Rates



Obama B. United States Health Care Reform Progress to Date and Next Steps. JAMA. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

## Republican Criticism of ACA

- Paul Ryan

- Speaker of House of Representatives

- Vice President nominee with Mitt Romney in 2012



## Republican Criticism of ACA

**“Congress is moving fast to rush through a health care overhaul that lacks a key ingredient: the full participation of you, the American people. I applaud these efforts - and have proposed legislation to achieve these shared goals. The question is not whether health care in America needs to be reformed; the question centers on how we achieve our shared reform goals. More critically: Who should be at the center of health care in America? Right now, the nucleus of power lies with third parties - insurers, employers and bureaucratic administrators. As we move forward with reform, should we shift the decision-making power to the federal government, or should we look to empower the patient and the doctor?”**

-Paul Ryan, *Milwaukee Journal Sentinel*, July 2009

## A Better Way



Health Care  
June 22, 2016  
[better.gop](http://better.gop)

Ryan, P. (2016). A better way: Our vision for a confident America. *Health Care*, 22.

## A Better Way

- Five Principles
- 1. Repeal Obamacare
- 2. Provide all Americans with more choices, lower costs, and greater flexibility
- 3. Protect our nation's most vulnerable
- 4. Spur innovation in health care
- 5. Protect and preserve Medicare

Ryan, P. (2016). A better way: Our vision for a confident America. *Health Care*, 22.



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## Republican Claims of ACA

- Patient choice of providers
- Society funded healthcare
- Individual Mandate
- Health Insurance Exchange enrollment
- Federalism fostering
- National Healthcare Expenditure & Gross Domestic Product (GDP)



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## The Past and Future of the Affordable Care Act

### The Past and Future of the Affordable Care Act

Jonathan Skinner, PhD, Amitabh Chandra, PhD

In this issue of *JAMA*, President Barack Obama has provided a comprehensive assessment of the Affordable Care Act (ACA),<sup>1</sup> which as he indicates is the most comprehensive health care reform since Medicare. In 1965, Medicare passed in the House with a 313-115 vote and in the Senate with a 68-21 vote. By contrast, the ACA barely reached the filibuster-proof threshold of 60 votes in the Senate and passed the House with a 219-212 vote. As President Obama has chronicled, that the ACA passed at all, let alone survived multiple Supreme

by \$1000 per person annually, and emergency department use increased by 40%.<sup>2,3</sup>

These findings from Oregon, in contrast to claims that were made to justify the ACA,<sup>4</sup> suggest both optimism and caution for the ACA's primary goal of expanding insurance coverage and the related consequences. Even Medicaid—an insurance program that offers lower payment rates and narrower networks than commercial insurers and Medicare—is valuable but possibly less valuable than had been hoped. In other words, providing health insurance may not automatically result in an improvement in health when health care systems are fragmented and inefficient.

Skinner, J., & Chandra, A. (2016). The past and future of the Affordable Care Act. *JAMA*, 316(5), 497-499.



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## The Past and Future of the Affordable Care Act

- Between 2010-2014, slowing of healthcare spending cannot be attributed to ACA
- Prior to ACA passage and 2008 recession, healthcare spending slowed
- Medicare enrollees insulated from higher payments and deductibles due to “exnovation” of costly treatments beginning in 2006



Skinner, J., & Chandra, A. (2016). The past and future of the Affordable Care Act. *JAMA*, 316(5), 497-499.

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## The Future of the Affordable Care Act Reassessment and Revision

### The Future of the Affordable Care Act Reassessment and Revision

Stuart M. Butler, PhD, MA

In this issue of *JAMA*, President Barack Obama describes many of the features and highlights the results of the Affordable Care Act (ACA).<sup>1</sup> Aligning federal payments more with demonstrated value and encouraging a move away from a fee-for-service model to managed care has helped reinforce or change the type of reimbursement patterns in the private sector. Allowing young adults to remain on their parents' insurance plan and curbing preexisting condition exclusions addressed significant problems. Creating exchanges was a key step toward allowing US residents to keep the health coverage they want as they move from job to job. Moreover, significantly reducing the number of uninsured households has brought improved care and a measure of financial security to millions of Americans.

her projections. Last year, Department of Health and Human Services Secretary Sylvia Burwell announced a sharply reduced goal for growth in exchange coverage in 2016: just 1.3 million compared with much higher earlier projections.<sup>2</sup> Moreover, the CBO now estimates that over the next 10 years, as the population increases, the number of people with coverage will expand only modestly, and the proportion of individuals uninsured will cease to decline.<sup>3</sup> A cause of the disappointing trend in exchange enrollment and the strong Medicaid growth is that the premiums and out-of-pocket exposure make exchange plans unattractive to many US residents. With subsidies focused on people with incomes near the poverty line, many middle class and modest-income households find they face substantial and uncertain costs if they enroll in exchange plans. Those choosing bronze plans to keep premiums low essentially have only catastrophic coverage. While that is an improvement over being

Butler, S. M. (2016). The future of the Affordable Care Act: Reassessment and revision. *JAMA*, 316(5), 495-497.

## The Future of the Affordable Care Act Reassessment and Revision

### • Exchange Plans

- Subsidies focused on incomes near poverty line
- Middle class is vulnerable in insurance exchange
- Coverage in name only

### • Subsidies

- “Family glitch” – legislative ambiguity excludes working families from exchange tax credits

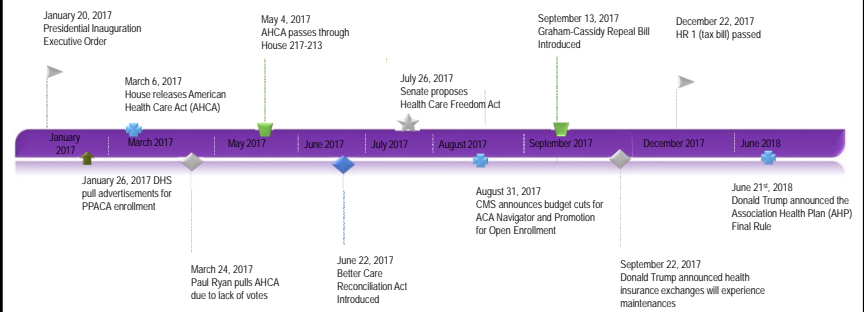
Butler, S. M. (2016). The future of the Affordable Care Act: Reassessment and revision. *JAMA*, 316(5), 495-497.

## What are some key issues regarding the ACA?

- Is healthcare a right or a privilege?
- Society funded healthcare
- Morality of government involvement
- Free market influence of healthcare reforms
- All of the above



## ACA 2017 Timeline



Rouds, R. (2017, September 26). TIMELINE: The GOP's failed effort to repeal ObamaCare. Retrieved February 02, 2018, from <http://thehill.com/policy/healthcare/352567-timeline-the-gop-effort-to-repeal-and-replace-obamacare>

## Efforts to Repeal, Replace, Reform the ACA



## Efforts to Repeal, Replace, Reform the ACA

- American Health Care Act
  - H.R. 1628
- Obamacare Repeal Reconciliation Act of 2017 (ORRA)
  - An amendment in the nature of a substitute to H.R. 1628

Kaiser Family Foundation. 2018, January 28. Retrieved from <http://files.kff.org/attachment/Proposals-to-Replace-the-Affordable-Care-Act-Summary-of-the-American-Health-Care-Act>  
Congress, U. S. (2017). H.R. 1628. Better Care Reconciliation Act. In 115th Congress (Vol. 2017).

## Efforts to Repeal, Replace, Reform the ACA

- Better Care Reconciliation Act of 2017
  - Congressional Budget Office (CBO) and Joint Committee on Taxation (JCT) cost estimate of AHCA
- Health Care Freedom Act
  - Proposed in the Senate as an amendment in the nature of a substitute to H.R. 1628

Kaiser Family Foundation. 2018, January 28. Retrieved from <http://files.kff.org/attachment/Summary-of-the-Health-Care-Freedom-Act>

## Efforts to Repeal, Replace, Reform the ACA

- Graham-Cassidy-Keller-Johnson Amendment
  - An amendment in the nature of a substitute to H.R. 1628
- H.R. 1 (tax bill)
  - December 22, 2017
  - Individual mandate repealed

Kaiser Family Foundation. 2018, January 28. Retrieved from <http://files.kff.org/attachment/Summary-of-the-Graham-Cassidy-Keller-Johnson-Amendment>  
U.S. Congress (2017) H.R. 1 - An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018. In 115th Congress (Vol. 2017).

## Trump Administration influence to disassemble ACA



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## Executive Order 13765

### Executive Order Minimizing the Economic Burden of the Patient Protection and Affordable Care Act Pending Repeal

- Intent to promote healthcare choice and competition across the United States
- Extend short-term coverage policies
- Expand coverage beyond state lines
- Call to coordinate efforts to disassemble the ACA through legal action
  - Department of Health and Human Services (DHS)
  - Internal Revenue Service
  - Congress

Office of the Press Secretary (January 20, 2017). "Executive Order Minimizing the Economic Burden of the Patient Protection and Affordable Care Act Pending Repeal". whitehouse.gov. United States.

## DHS Advertisements

- Trump administration pulled open enrollment advertisements for ACA enrollment prior to January 31, 2017 open enrollment deadline

Rouben, R. (2017, September 26). TIMELINE: The GOP's failed effort to repeal ObamaCare. Retrieved February 02, 2018, from <http://thehill.com/policy/healthcare/352587-dmeline-the-gop-effort-to-repeal-and-replace-obamacare>

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## Health Insurance Exchange

- Trump administration announced the Healthcare.gov enrollment would close on November 1, 2017 (first day of open enrollment)
- Scheduled maintenances
  - Health insurance exchanges shut down midnight to noon every Sunday during open enrollment except December 10, 2017

Mohrney, M. (2017). America First: A Budget Blueprint to Make America Great Again. The White House. Centers for Medicare and Medicaid Services. 2017, August 16. CMS Announcement on ACA Navigator Program and Promotion for Upcoming Open Enrollment (Press Release). Retrieved from <https://www.cms.gov/ResearchandStatisticsandData/Press-releases/2017-08-16-3.html>



## Association Health Plan Final Rule

- Association Health Plans (AHP)
  - Group health plans that employer groups and associations offer to provide health coverage for their members' employees
  - New and existing pathways
- Department of Labor Employee Benefits Security Administration
  - Definition of "Employer"

Department of Labor. Employee Benefits Security Administration 29 CFR Part 2510



## What part of ACA did the H.R.1 (tax bill) repeal since its passage on December 22, 2017?

- A. Ten essential health benefits
- B. Individual mandate
- C. Medicare/Medicaid expansion
- D. Cadillac tax
- E. Large employer mandate



## Objectives

1. Outline key provisions of the Patient Protection and Affordable Care Act
2. Explain support and criticism for the Patient Protection and Affordable Care Act
3. Explain efforts to date of the Congress to repeal, replace, and reform the PPACA and describe current efforts to revise the law

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## House of Cards: The In and Out of the Patient Protection and Affordable Care Act

Joelle Farano, PharmD  
The University of Chicago Medicine  
September 14<sup>th</sup>, 2018



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# Revolutionizing the Pharmacy Supply Chain

Trac Pham, R.Ph., MS, MBA  
Director, Integrated Service Center Pharmacy  
Advocate Aurora Health

The speaker has no conflicts of interest to disclose.

## Learning Objectives – Pharmacist and Technician

- State services provided by an Integrated Service Center (ISC)
- Explain how technology can be leveraged to manage inventory
- Describe potential cost savings from streamlining inventory

**What is the greatest challenge facing your pharmacy operations today?**

## THIS IS transformation Advocate Aurora Health

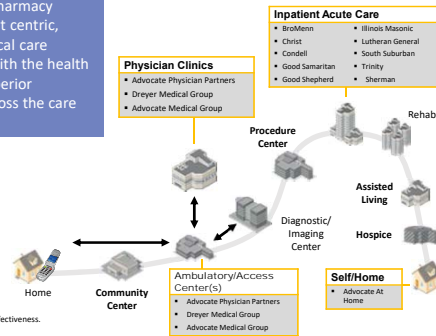
By the numbers



## THE NEW WORLD

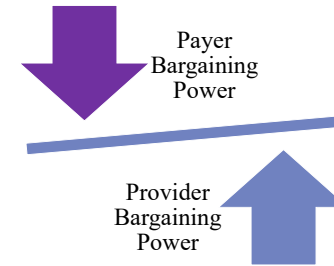
### Mergers, Consolidation & Centralization

Advocate Health Care Pharmacy Services provides patient centric, innovative pharmaceutical care through collaboration with the health care team to deliver superior outcomes and value across the care continuum.



## “WINNING VS. LOSING”

### Leverage



## REASONS FOR ACTION

Issues	Description	Initial Est. System Impact	YTD June 2018 Savings Results
Inefficiency	Lack of pharmacy inventory backbone / automation leading to: <ul style="list-style-type: none"> <li>Incomplete understanding of inventory <ul style="list-style-type: none"> <li>Asset value</li> <li>Utilization / Days on hand</li> <li>Reorder Points &amp; Reorder Quantities</li> </ul> </li> </ul>	\$900K – additional cost	\$1.6M
	Lack of a system automated repackaging process		\$3.2M
Redundancy & Lack of Standards	Ten separate pharmacy buyers performing the same duplicative functions across the systems	\$300K – additional cost	\$770K; plus central procurement for 4 sites
	Lack of production standardization which leads to increased risk for errors and higher costs.		
Economies of Scale	Pharmacy did not fully leverage our size as an organization for strategic purchasing (high cost- low use, forward buys/spee buys, bulk buys, etc.)	\$900K – incremental cost	\$4.1M
	Buying Power – leveraging Advocate's intel and buying power for better pricing	\$555???	

## SOLUTION: A Centralized Integrated Approach

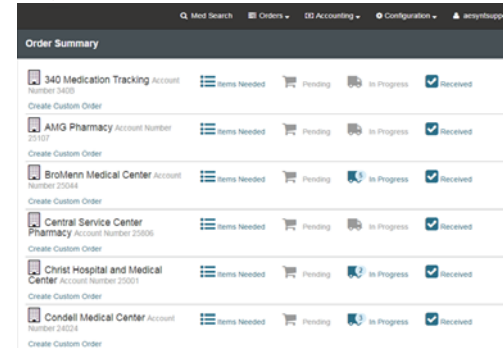
Centralized pharmacy integrated supply center with pharmacy automation and software for enterprise inventory management.

Standardized	Implemented	Centralized	Partnered
<ul style="list-style-type: none"> <li>Placed all inpatient pharmacies on a standard inventory technology platform (Enterprise Medication Manager)</li> </ul>	<ul style="list-style-type: none"> <li>Installed automation at all inpatient pharmacies to provide a true closed perpetual inventory management system (MedCarousels / MedShelves).</li> </ul>	<ul style="list-style-type: none"> <li>Centralized the ordering of key medications.</li> <li>Centralized the pre-packaging of medications (PacMeds).</li> <li>Centralized and in-sourced key IV medications (Repeater Pumps).</li> </ul>	<ul style="list-style-type: none"> <li>Established regional partnerships to optimize existing technologies and processes.</li> </ul>

## Which has enabled specific ISC Programs...

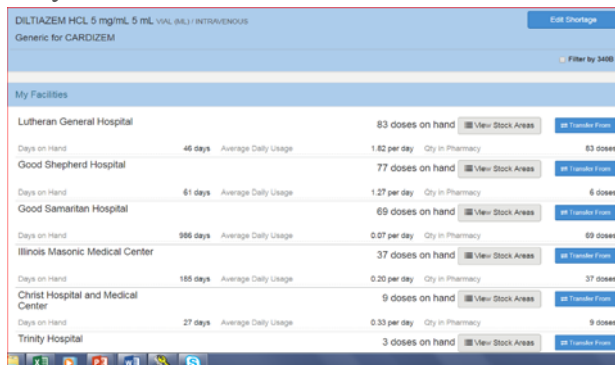
- Inventory Optimization / Reduction
- Low Unit-of-Measure (LUM) Distribution
- Central Unit-Dose Packaging
  - Oral solids (Central-fill Robots and ADCs )
  - Oral Liquids
  - IVs
  - Kits (Epi & HIV PEP)
- Strategic Buying
  - Forward buys
  - Opportunity buys
  - Speculative buys
- Drug Shortage Mitigation
- 340B Penny Buys
- Central Procurement (4 sites)

## SOLUTION: Innovative Technology Key to Innovative Success

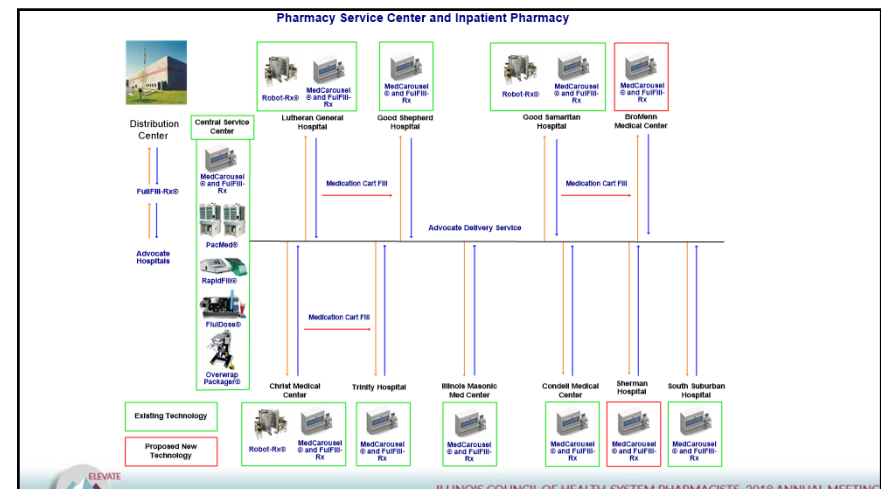


Account Number	Account Name	Status	Actions
340 Medication Tracking Account Number 3403		Items Needed	Pending
AMG Pharmacy Account Number 23107		Items Needed	Pending
Bromann Medical Center Account Number 23044		Items Needed	Pending
Central Service Center Pharmacy Account Number 25006		Items Needed	Pending
Christ Hospital and Medical Center Account Number 25001		Items Needed	Pending
Condell Medical Center Account Number 24024		Items Needed	Pending

## SOLUTION: Innovative Technology Key to Sustainable Success

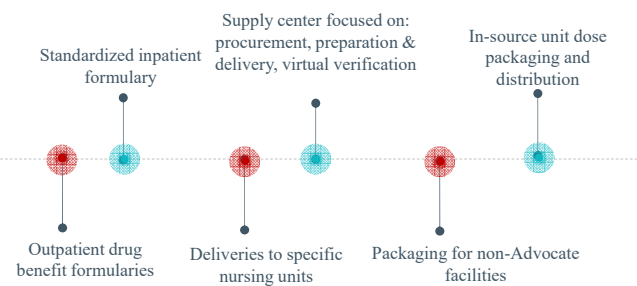


Facility	Doses on Hand	Average Daily Usage	City in Pharmacy
Lutheran General Hospital	83 doses on hand	1.82 per day	City in Pharmacy
Good Shepherd Hospital	77 doses on hand	1.27 per day	City in Pharmacy
Good Samaritan Hospital	69 doses on hand	0.07 per day	City in Pharmacy
Illinois Masonic Medical Center	37 doses on hand	0.20 per day	City in Pharmacy
Christ Hospital and Medical Center	9 doses on hand	0.33 per day	City in Pharmacy
Trinity Hospital	3 doses on hand		City in Pharmacy



## Roadmap to Growth and Success

Standardization, Consolidation & Full Inventory Visibility



## BEFORE

Site Inpatient Pharmacy



## AFTER

Site Inpatient Pharmacy



## INTEGRATED SERVICE CENTER



## INTEGRATED SERVICE CENTER



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## INTEGRATED SERVICE CENTER



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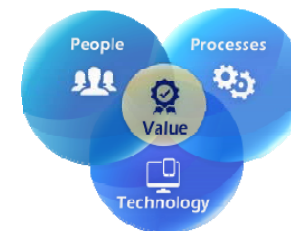
## INTEGRATED SERVICE CENTER



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## SUSTAINABLE AND SCALABLE



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## 360° COLLABORATIVE PARTNERSHIPS

Key to Sustainable Success

### Internal Partners

- Senior Leaders
- Front-line Staff
- Supply Chain Management
- Operations Management
- Nursing

### External Partners

- Omnicell (software, hardware, & consultation)
- Owens & Minor
- McKesson Distribution
- MedSpeed

## RESULTS – YTD June 2018

Improved Turns & Days on Hand

Exceeded inventory turn goal in a little over a year

The higher the turns – the smaller the on-hand inventory investment. Affords ability to free up funds for other investments.

Potential added benefit – decrease expired meds.



Average Inventory Turns  
**19.05**

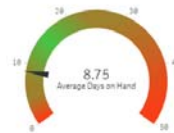


## RESULTS

### ABC Inventory Optimization

Medications contributing to the top **80%** of the overall drug spend maintain inventory levels of **<9** days on-hand and **>41** Turns/year.

Average Inventory Turns  
**41.70**



On average around 200 medications contribute to approximately 80% of the total drug spend. Managing those items more closely leads to less money tied up in inventory at any given time.

## RESULTS

### Total Savings / Cost Avoidance

Over **\$26M** savings/cost avoidance in just over 3 years

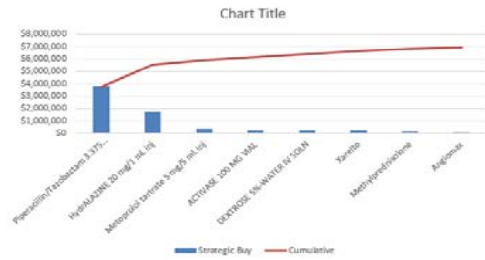
System Savings attributed to strategic purchases, repacking business, low unit of measure distribution, 340B "penny" purchases, and inventory reduction.



## RESULTS

### Strategic Buy Savings

Over **\$10.9M** in bulk buy savings since inception!

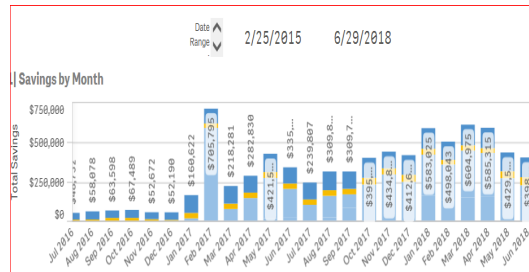


Strategically purchasing product in bulk to access additional manufacturer discounts, delay impact of price increases, and better manage shortages.

## RESULTS

### Central Packaging Savings

Over **\$8.1M** in central packaging savings in just over 3 years



Centralized oral solid, oral liquid, and some IV compounded medications along with preparing specific kits to gain efficiency and save dollars across the organization.

## RESULTS

### Inventory Reduction Savings

Over **\$1.6M** in inventory reduction savings in just over 1 year



Optimize on-hand inventory across the health system; improve cash flow.

## RESULTS

### Net Savings

Over **\$10.2M** net savings in 2016-2017

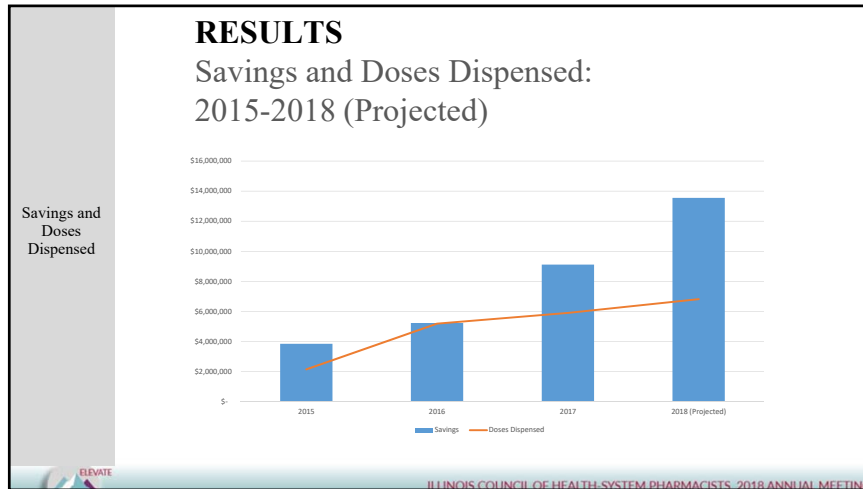


Factoring in the expenses of the ISC, we still see a tremendous amount of net savings from the operation which translates into a significant savings on every single dose we distribute.

**\$0.92 net savings on every dose shipped!**

Savings per Dose Shipped:	\$1.29	Expense per Dose Shipped:	\$0.36	Net Savings per Dose Shipped:	\$0.92
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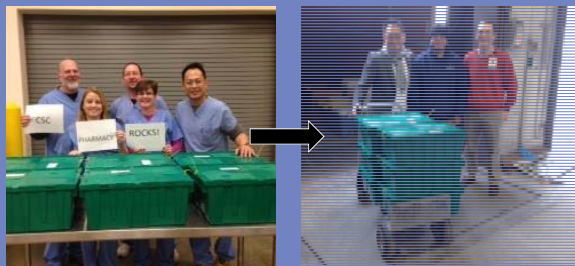


# \$26,205,726

Cost Savings/Avoidance in just over 3 years

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- ## Recap Learning Objectives
- State services provided by an Integrated Service Center (ISC)
  - Explain how technology can be leveraged to manage inventory
  - Describe potential cost savings from streamlining inventory



**“If you build it...they will come.”**



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**Have fun!**

**Questions?**

You can find me at:

[trac.pham@advocatehealth.com](mailto:trac.pham@advocatehealth.com)



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## Pharmacist Contraceptive Prescribing: A Therapeutic Review and Illinois Status Update

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The speakers have no conflicts of interest to declare.



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## Learning Objectives - Pharmacists

1. Compare available hormonal contraceptive products, patient eligibility, and resources needed to incorporate contraceptive prescribing into practice.
2. Given a patient case, utilize the MEC, the Pharmacist's Patient Care Process, and other available resources to create and implement a comprehensive patient contraceptive plan.
3. Discuss current and pending legislation in Illinois and other states and review experiences of pharmacist contraceptive prescribing implementation.



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## Objective

Compare available hormonal contraceptive products, patient eligibility, and resources needed to incorporate contraceptive prescribing into practice

**Daniel Majerczyk, PharmD, BCPS, BC-ADM, CACP**

Assistant Professor of Clinical Sciences  
Roosevelt University College of Pharmacy



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## Which of the following is one of the most effective forms of contraception available?

The implant

The patch

The ring

The condom



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**A contraindication to initiating a combined hormonal contraceptive is:**

- A migraine without aura and age <35 years old
- Smoking 2 packs per day and age <35 years old
- Sickle cell disease
- Blood pressure of 162/90 mmHg

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**To confirm patient's appropriateness of initiating or continuing a contraceptive method, the pharmacist would consult which one of the following resources?**

- The Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use (MEC)
- The Pharmacy Practitioners Patient Care Process
- The Guidelines for Providing Hormonal Contraception
- The Assessment Procedure for Prescribing Hormonal Contraceptives

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## Background

- About 45% of pregnancies in the United States are unintended.
- Access to contraception is one of the biggest barriers.
- Pharmacists can assist patients seeking contraception in many ways including educating them on the risks/benefits of available products, assisting patients on selecting the most appropriate method of contraception, and in some states, prescribing.
- Some states have successfully implemented legislation authorizing pharmacists to prescribe self-administered hormonal contraception and legislation in Illinois is currently pending.
- Practicing pharmacists in Illinois may not be familiar with the potential processes, products, and counseling that is included in this pending legislation.

Finer LB and Zolna MR, Declines in unintended pregnancy in the United States, 2008–2011. *New England Journal of Medicine*, 2016, 374(9):843–852. <http://nejm.org/doi/full/10.1056/NEJMma1506575>

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## Hormonal Contraceptive Products

### Pharmacology

- Mechanism of Action (MOA)
- Description of how hormonal contraceptive products affect phases of the menstrual cycle

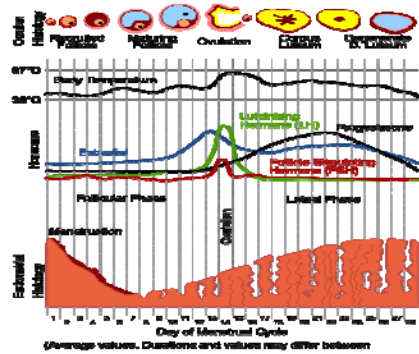
### Key features of agents

- Progestin content and effect
- Estrogen content and effect
- Combined
  - Progestin and estrogen

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## The Menstrual Cycle



(Average values. Individual values may differ between different females or different cycles.)

Picture source: [https://commons.wikimedia.org/wiki/File:MenstrualCycle\\_en.svg](https://commons.wikimedia.org/wiki/File:MenstrualCycle_en.svg)

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## Mechanism of Action (MOA)

### Progesterone

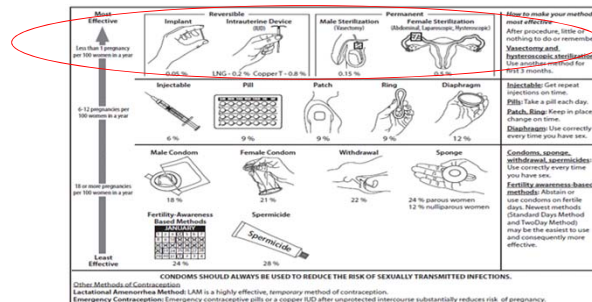
- Thickens the cervical mucus
  - Making it harder for the sperm to penetrate
- Decreases the likelihood of implantation
- Inhibit an estrogen-induced luteinizing hormone (LH) surge at mid cycle from the anterior pituitary

### Estrogen

- Inhibits the release of follicle-stimulating hormone (FSH) and LH from the anterior pituitary
- Stabilizes the endometrial lining
- Decreases breakthrough bleeding

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## Contraception Forms and their Efficacy



Other Methods of Contraception:  
 Lactational Amenorrhea Method (LAM) is a highly effective, temporary method of contraception.  
 Emergency Contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.  
 Adapted from World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD: Geneva, Switzerland: CCP and WHO; 2011; and Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397-404.  
 Curtis KM, Tepper NK, Jatavou TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-3):1-104. DOI: <http://dx.doi.org/10.15585/mmwr.mm6503a1>. Accessed August 8, 2018.

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## Classification of Progestins

### Progestins

#### C-21 progestins

- Medroxyprogesterone acetate
- Megestrol acetate
- Cyproterone acetate

#### 19-nor testosterone

- Estranes
  - Norethindrone
  - Norethindrone acetate
  - Norethynodrel
- Gonanes
  - Norgestrel
  - Levonorgestrel
  - Norgestimate
  - Desogestrel
  - Gestodene

#### Spirolactone

- Drospirenone

Amiri M, Ramezani Tehrani F, Nahidi F, Kabir A, Azizi F. Comparing the Effects of Combined Oral Contraceptives Containing Progestins With Low Androgenic and Androgenic Activities on the Hypothalamic-Pituitary-Gonadal Axis in Patients With Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. Eysenbach G, ed. JMIR Research Protocols. 2018;7(4):e113. doi:10.2196/resprot.9024.

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## Different Forms of Progestin in CHC Pills

	Progestin	Estrogen	Androgen
Desogestrel	++++	0	+++
Levonorgestrel	++++	0	++++
Norgestrel	+++	0	+++
Drospirenone	++	0	0
Ethinodiol Acetate	++	+++	+
Norgestimate	++	0	++
Norethindrone	++	++	++
Norethindrone acetate	++	++	++
Dienogest	+	0	0

Zapata LB, Steenland MW, Brahmi D, Marchbanks PA, Curtis KM. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review. Contraception. 2013;87(5):685-700. doi:10.1016/j.contraception.2012.08.035.

## CHC Products

- **Oral formulation**
  - 1 tab po qd
- **Transdermal formulation**
  - Apply 1 patch qwk x 3wk, off x 1wk
- **Vaginal ring**
  - 1 ring PV x 3wk, off x 1wk

## Progestin Only Contraceptives

- **Progestin Only Pills (POPs)**
  - "Mini-Pill"
  - Norethindrone 0.35 mg Tabs
  - Must be taken at the same time each day
  - If you miss a pill for more than 3 hours
    - Must use back-up contraception for the next 48 hours
- **Injectable**
  - IM and SC
  - 3 months of contraception
- **Implant**
  - Long acting and reversible
  - 3 years of contraception
  - Office visit for implantation and removal
- **Intrauterine device (IUD)**
  - Long acting and reversible
  - Levonorgestrel
  - Up to 5 years of contraception depending on the device
  - Office visit for placement and removal

## Non-Contraceptive Benefits of Hormonal Contraceptives

- **Medicating the symptoms of dysmenorrhea**
  - Painful/difficult menses
- **Reducing the frequency and length of the menstrual cycle**
- **Reducing menorrhagia**
  - Heavy menstrual bleeding
- **Reducing the rates of some cancers**
  - Ovarian
  - Endometrial
- **Improving certain skin conditions**
  - Acne

## Initial Counseling

- Contraceptive counseling should aim to maximize:
  - Efficacy
  - Patient satisfaction
  - Long-term adherence
- Selecting an appropriate contraceptive method requires:
  - Complete medical history
    - Focus on ruling out the most common contraindications
  - The World Health Organization (WHO)
    - Absolute and relative contraindications to the different contraceptive methods

## Medical Eligibility for Initiating Contraception: Absolute and Relative Contraindications

Risk Level	
1	Method can be used without restriction
2	Advantages generally outweigh theoretical or proven risks
3	Method not usually recommended unless other, more appropriate methods are not available or not acceptable
4	Method not to be used

These contraceptive methods do not protect against sexually transmitted infections (STIs). Condoms should be used to protect against STIs. For more information, see [who.int/reproductivehealth/publications/family\\_planning/9789241563888/en/index.html](http://www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html), [cdc.gov/mmwr/preview/mmwrhtml/rr5005a1.htm?\\_id=rr5005a1&\\_e\\_cdc.gov/mmwr/preview/mmwrhtml/mm6008a2.htm?\\_id=mm6008a2\\_e\\_cdc.gov/mmwr/preview/mmwrhtml/m6205a1.htm?\\_id=m6205a1\\_Lw](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5005a1.htm?_id=rr5005a1&_e_cdc.gov/mmwr/preview/mmwrhtml/mm6008a2.htm?_id=mm6008a2_e_cdc.gov/mmwr/preview/mmwrhtml/m6205a1.htm?_id=m6205a1_Lw), <http://www.aacog.org/Resources-and-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Adolescents-and-Long-Acting-Reversible-Contraception>, <http://pediatrics.aappublications.org/content/early/2014/09/24/peds.2014.1299.full.pdf>

Condition	Qualifier for condition	Estrogen/ progestin: pill, patch, ring	Progestin- only pill	Progestin- only injection	Progestin- only implant	Progestin IUD	Copper IUD
Age	< 18	1	1	2	1	1	1
	18-30	1	1	1	1	1	1
	31-45	2	1	1	1	1	1
Anemia	> 15	2	1	2	1	1	1
	Thalassemia	1	1	1	1	1	2
	Sickle cell disease	2	1	1	1	1	2
Bariatric surgery	Iron-deficiency anemia	1	1	1	1	1	2
	Stomach restrictive procedures, including lap band	1	1	1	1	1	1
	Malabsorptive procedures, including gastric bypass	Pill: 3 Patch or ring: 1	3	1	1	1	1
Breast cancer	Family history of cancer	1	1	1	1	1	1
	Current	4	4	4	4	4	1
	In past, no evidence of disease for > 5 years	3	3	3	3	3	1

ReproductiveAccess. ReproductiveAccess Online Web Site. Available at: <https://www.reproductiveaccess.org/resource/medical-eligibility-initiating-contraception/>. Accessed August 7, 2018.

## Medical Eligibility for Initiating Contraception: Absolute and Relative Contraindications

Condition	Qualifier for condition	Estrogen/ progestin: pill, patch, ring	Progestin- only pill	Progestin- only injection	Progestin- only implant	Progestin IUD	Copper IUD
Depression		1	1	1	1	1	1
	Gestational DM in past	1	1	1	1	1	1
	Diabetes mellitus (DM)						
Diabetes mellitus (DM)	DM without vascular disease	2	2	2	2	2	1
	DM with end-organ damage or > 20 years duration	3	2	3	2	2	1
Drug Interactions	Antiretrovirals	All antiretroviral medications (except fosamprenavir) are either 1 or 2 for every contraceptive method.					
	Anticonvulsants: phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine	3 Must select a pill with a 30 mcg of estrogen to maximize efficacy	3	1	2	1	1
	Lamotrigine alone (Lamotrigine/valproate combo does not interact with hormones)	3	1	1	1	1	1
	Rifampin/rifabutin	3	3	1	2	1	1
	ALL OTHER antibiotics, antiparasitics, & antifungals	1	1	1	1	1	1

ReproductiveAccess. ReproductiveAccess Online Web Site. Available at: <https://www.reproductiveaccess.org/resource/medical-eligibility-initiating-contraception/>. Accessed August 7, 2018.

## Pharmacist's Role in Assessing Women for Hormonal Contraception

- Provide access to prescription and OTC products
- Advise patients about:
  - Appropriate selection and use of contraceptive products
  - What to do in the event of missed pills, or delayed start
  - Provide counseling when there is a potential of drug interactions or when side effects are reported

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Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65(No. RR-3):1–104. DOI: <http://dx.doi.org/10.15585/mmwr.r6503a1>.

Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65(RR-3):1–104. DOI: <http://dx.doi.org/10.15585/mmwr.r6503a1>.



## How to Interpret the MEC

Safety/Risk Categories	
1	Method can be used without restriction
2	Advantages generally outweigh theoretical or proven risk
3	Method usually not recommended unless other, more appropriate methods are not available or not acceptable
4	Method not to be used

Use the method

Do not use the method

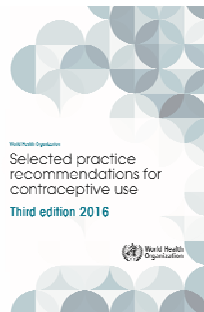
Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-3):1-104. DOI: <http://dx.doi.org/10.15585/mmwr.rr6503a1>.

## How to Interpret the MEC

Condition	Sub-condition	Copper - IUD	LNG - IUD	Implant	Injection	Progestin-only pill	Combined pill, patch, ring
Obesity	a) Body mass index (BMI) $\geq 30$ kg/m <sup>2</sup>	1	1	1	1	1	2
	b) Menarche to <18 years and BMI $\geq 30$ kg/m <sup>2</sup>	1	1	1	2	1	2

Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-3):1-104. DOI: <http://dx.doi.org/10.15585/mmwr.rr6503a1>.

## Guidelines for Providing Hormonal Contraception



New clinical recommendations	GRADE assessment of quality of evidence	Strength of recommendation
<b>1. Levonorgestrel (LNG) Intrauterine System (IUS)</b>		
1.1 A woman can start LNG IUS within 7 days after the start of her menstrual bleeding. She can also start at any other time if it is reasonably certain that she is not pregnant. Recommendations are also provided for other additional precautions needed and for women who are amenorrheic, postpartum, post-abortion, switching from another method.	No direct evidence	Strong
1.2 It is desirable to have blood pressure measurements taken before initiation of IUS. Women should not be denied use of IUS simply because their blood pressure cannot be measured.	No direct evidence	Strong
1.3 Breast examination to provide, pelvic/sexual examination, cervical cancer screening, routine laboratory tests, hemoglobin test, sexually transmitted infection (STI) risk assessment (medical history and physical examination) and STI/RH screening (laboratory tests) do not contribute substantially to the safe and effective use of IUS.	No direct evidence	Strong
1.4 The product labelling for IUS states that the implant can be left in place for up to 5 years.	Low	Strong
1.5 The product labelling for IUS states that the implant can be left in place for up to 5 years.	No direct evidence	Strong
<b>2. Progestin-only Injections (POI)</b>		
2.1 A woman can start POI within 7 days after the start of her menstrual bleeding. She can also start at any other time if it is reasonably certain that she is not pregnant. Recommendations are also provided for other additional precautions needed and for women who are amenorrheic, postpartum, post-abortion, switching from another method.	No direct evidence	Strong
2.2 It is desirable to have blood pressure measurements taken before initiation of POI. Women should not be denied use of POI simply because their blood pressure cannot be measured.	No direct evidence	Strong
2.3 Breast examination to provide, pelvic/sexual examination, cervical cancer screening, routine laboratory tests, hemoglobin test, STI risk assessment (medical history and physical examination) and STI/RH screening (laboratory tests) do not contribute substantially to the safe and effective use of POI.	No direct evidence	Strong
2.4 Provide repeat POI injections every 3 months. Recommendations are also provided for early and late injections.	Very low	Strong

Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-4):1-66. DOI: <http://dx.doi.org/10.15585/mmwr.rr6504a1>.

## Selected Practice Recommendations for Examination and Tests Needed

Exam or Test	Progestin Only Injection and Oral Tablets	Combined Hormonal Contraceptives
Blood pressure	C	A <sup>1</sup>
Weight	†	†
Breast exam	C	C
Bimanual exam/cervical inspection	C	C
Blood glucose	C	C
Serum lipids	C	C
Liver enzymes	C	C
Thrombotic mutations	C	C
Papanicolaou (PAP) test	C	C
STD Screening	C	C
HIV Screening	C	C

Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-4):1-66. DOI: <http://dx.doi.org/10.15585/mmwr.rr6504a1>.

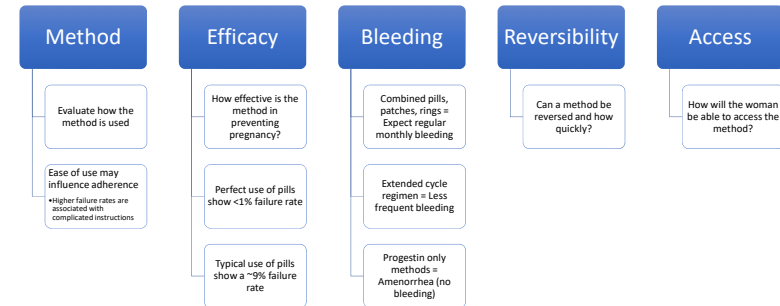
## Assessing Blood Pressure

Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
	I	C	I	C	I	C	I	C	I	C	I	C
Hypertension												
a) Adequately controlled hypertension	1*		1*		1*		2*		1*		3*	
b) Elevated blood pressure levels (properly taken measurements)												
i) Systolic 140-159 or diastolic 90-99	1*		1*		1*		2*		1*		3*	
ii) Systolic ≥160 or diastolic ≥100†	1*		2*		2*		3*		2*		4*	
c) Vascular disease	1*		2*		2*		3*		2*		4*	

Curtis KM, Tepper NK, Jattaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-3):1-104. DOI: <http://dx.doi.org/10.15585/mmwr.r6503a1>.

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## What to Consider When Selecting and Initiating a Hormonal Contraceptive Regimen



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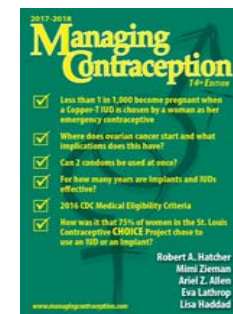
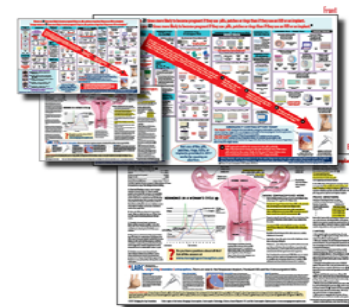
## Pill, Patch & Ring Warning Signs - ACHES

ABDOMINAL PAIN	CHEST PAIN	HEADACHES	EYE PROBLEMS	SEVERE LEG PAIN
Clot in the pelvis or liver (mesenteric or pelvic-vein thrombosis)	Clot in the lung or heart vessels (pulmonary embolism [PE] or myocardial infarction [MI])	Stroke	Stroke or retinal vein thrombosis	Inflammation and blood clots of a leg in the leg
Vomiting	Heart attack, angina	Blurred vision, spots, zigzag lines, weakness, difficulty speaking	Complete or partial loss of vision	Swelling, heat or redness, tenderness in leg
Cramping	Chest or heart pain, left arm and shoulder pain	Sudden intellectual impairment		
Weakness	Coughing and shortness of breath			

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## Managing Contraception Resources:

[managingcontraception.com](http://managingcontraception.com)



Picture Sources: <http://managingcontraception.com>. With full permission. Accessed August 8, 2018.

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**Which of the following is one of the most effective forms of contraception available?**

- The implant
- The patch
- The ring
- The condom

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**To confirm patient's appropriateness of initiating or continuing a contraceptive method, the pharmacist would consult which one of the following resources?**

- The Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use (MEC)
- The Pharmacy Practitioners Patient Care Process
- The Guidelines for Providing Hormonal Contraception
- The Assessment Procedure for Prescribing Hormonal Contraceptives

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**A contraindication to initiating a combined hormonal contraceptive is:**

- A migraine without aura and age <35 years old
- Smoking 2 packs per day and age <35 years old
- Sickle cell disease
- Blood pressure of 162/90 mmHg

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**Objective**

Given a patient case, utilize the MEC, the Pharmacist's Patient Care Process, and other available resources to create and implement a comprehensive patient contraceptive plan

**Kathleen M. Vest, PharmD, CDE, BCACP**  
 Professor of Pharmacy Practice  
 Northwestern University Chicago College of Pharmacy

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### Which of the patients would be an appropriate candidate for the contraceptive patch?

A 25 year old patient that smokes 15 cigarettes per day, and does not have any health conditions or medications.

A 42 year old patient with migraines with aura and no other medical conditions.

A 31 year old patient with epilepsy that takes carbamazepine.

A 29 year old patient with hypothyroidism.

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## Formulating a contraceptive plan for a patient

### Utilize Available Resources

- CDC MEC and SPR
- A resource listing contraceptive options
  - Hormonal:
    - Estrogen/progesterone: Pill, patch, ring
    - Progesterone only: Pill, injection, levonorgestrel intrauterine device (IUD)
  - Non-hormonal:
    - Copper IUD, sponge, diaphragm, condoms

### Be Aware of

- Products you can/cannot prescribe in your state
- Patient considerations and preferences
- Potential red flags, reasons for referral

Remember to counsel on STD prevention!

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## Pharmacists Patient Care Process

**Pharmacists' Patient Care Process**

**Pharmacists' Patient Care Process**  
Pharmacists use a patient-centered approach in collaboration with other providers on the health care team to optimize patient health and medication outcomes.

Using principles of evidence-based practice, pharmacists:

- Collect**  
The pharmacist ensures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.
- Assess**  
The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care.
- Plan**  
The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.
- Implement**  
The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.
- Follow-up: Monitor and Evaluate**  
The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.

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## Application of HC prescribing

### Collect

- Consider requirements for your state
- Interview patient, gather information

### Assess

- Utilize MEC, algorithms, drug information resources available
- What can you do in your state?

### Plan

- Work with patient to formulate plan
- Consider efficacy, cost, patient preferences
- Sometimes the plan will be to refer to the provider

### Implement

- Patient education
- Documentation and communication with other providers

### Follow up and monitoring

- What, when, and who to follow up with
- Referral to other provider(s) if needed
- Be an advocate for your patients

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Which of the following would you recommend for Susan today?

Combined hormonal contraceptive pill

Patch

Refer to physician

Progestin only pill

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## Implementing the Plan

- Provide prescription:
  - COC pill, low androgen component
  - Documentation and communication with provider
- Counsel on:
  - ACHES
  - Directions for use, what to do if missed doses
  - STD prevention
  - Folic acid



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## Follow up and Monitoring

- Communication to providers
  - Standardized forms
  - Faxed form, phone call, patient sends information
  - Include your name and contact information
- Additional communication with the patient
  - Provide guidance for the patient for when to return
    - Consider quantity prescribed/when patient will seek a refill
    - Ensure patient knows how to reach you
  - Encourage her when to follow up the provider for screenings, etc.



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## Continued Follow Up: Susan returns 6 months later

- She is taking the combined oral contraceptive pill.
- However, she was in urgent care for headaches last week.
- She has been diagnosed with migraines with aura and now takes sumatriptan as needed, typically 3-5 times per month.
- She was told by the urgent care provider that she may need to change to an alternative contraceptive product.
- Next steps?



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### Which of the following would you recommend for Susan today?

Continue current regimen.

Switch to the patch.

Switch to a POP.

Stop current method, refer to MD.

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### Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

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### Case 2: Beth

"Hi, I heard I can get my birth control at the pharmacy now. Can you help me?"

Medical information collected

- 30 y/o female. Medical conditions: Asthma, epilepsy.
- Current medications: Albuterol, montelukast, lamotrigine
- LMP: 8/20/18

Patient preferences/factors

- Non-smoker; does not drink alcohol
- She is open to the pill, patch, or ring.

Physical assessment

- BMI: 29. Blood pressure: 120/72

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### What is your recommendation for Beth?

Combined hormonal contraceptive pill

Ring

Progestin only pill

Refer to her physician

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## Implementation, follow up and monitoring

### Plan

- Work with patient to formulate plan, provide prescription. Consider efficacy, cost, patient preferences
- Documentation and communication

### Implement

- Patient education: ACHES, dosing of medication
- Documentation, prescription, communicating with provider

### Follow up and monitoring

- What, when, and who to follow up with

## Beth

- Beth returns to the pharmacy 11 months later.
- She was taken off lamotrigine and is now on carbamazepine.
- She is wondering if her contraceptive plan needs to change based on the change to her epilepsy medications
- She does find it difficult to remember taking the pill every day and is wondering if she could try the patch or another type of product.

### What is your recommendation for Beth today?

Continue present management with POP

Switch to COC

Switch to patch

Review the benefits/risks of the IUD or medroxyprogesterone acetate, refer to MD

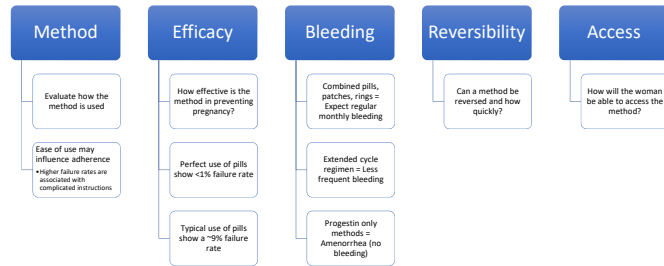
## Beth: Next steps

- How do you implement this plan for Beth?



## Summary

### What to Consider When Selecting and Initiating a Hormonal Contraceptive Regimen



## Key Takeaways

- Utilize the MEC and SPR to help determine an appropriate contraceptive method for a specific patient
- Consider patient's medical conditions, medications, and personal preferences when formulating the plan.
- Pharmacists have an important role in increasing patient access to contraception.

### Which of the patients would be an appropriate candidate for the contraceptive patch?

A 25 year old patient that smokes 15 cigarettes per day, and does not have any health conditions or medications.

A 42 year old patient with migraines with aura and no other medical conditions.

A 31 year old patient with epilepsy that takes carbamazepine.

A 29 year old patient with hypothyroidism.

## Objective

Discuss current and pending legislation in Illinois and other states and review experiences of pharmacist contraceptive prescribing implementation

**Brooke L. Griffin, PharmD, BCACP**

Professor and Vice Chair, Pharmacy Practice  
Midwestern University Chicago College of Pharmacy

### What is the status of a Pharmacist Contraceptive Prescribing bill in Illinois?

This bill has successfully passed in Illinois

This bill has not been proposed in Illinois

This bill is drafted and will be reviewed soon

I don't know the status of this bill in Illinois

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### Which of the following is potentially the largest barrier to pharmacist-prescribed contraception in Illinois?

Reimbursement

Provider acceptance

Workflow implementation

Pharmacist interest

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## Current and Future Opportunities for Pharmacists with Contraception in Illinois

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### Current and Future Opportunities for Pharmacists with Contraception in Illinois

**here & Now**

- Education/Counseling/Monitoring
  - Assess a woman's eligibility for hormonal contraception
  - Compare/contrast available options
  - Provide education and counseling related to side effects, drug interactions and missed doses
- With collaborative practice agreements:
  - Selecting an agent
  - Switching methods
  - Managing drug interactions

**FUTURE**

- Pharmacist provided contraception
  - Assess a woman's eligibility for hormonal contraception
  - Compare/contrast available options
  - Provide education and counseling related to side effects, drug interactions and missed doses
  - Provide access to contraceptive products within the scope of practice

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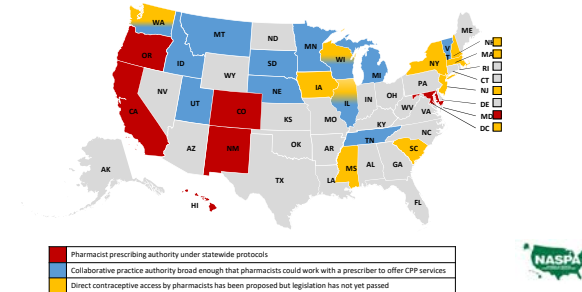
## Literature Review

### • Direct Access Study (2003)

- Objective: Determine the effectiveness of pharmacist prescribed contraceptives on patient continuation rates
- Results showed community pharmacists were able to efficiently provide screening with high resultant continuation rates
- Both women and pharmacists reported high levels of satisfaction with the service, and women were willing to pay out of pocket for the convenience of a pharmacist's prescribing their contraceptives.

Gardner JS, Downing DF, Blough D, Miller L, Le S, Shotorbani S. Pharmacist prescribing of hormonal contraceptives: results of the Direct Access study. JAPHA. 2008; 48(2):212-226

## Pharmacist Contraception Prescribing Status by State



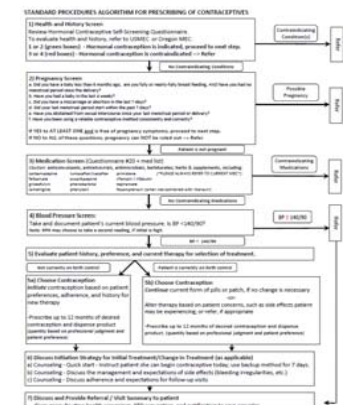
Kooner M, Joseph H, Griffin BL, Vest KM, Lynch SE, Stewart-Lynch A, Weaver K. Hormonal Contraceptive Prescribing by Pharmacists: 50 States Overview. Presented at the Pharmacy Quality Alliance Annual Meeting, Baltimore, MD, May 2018

## State Highlights

### Oregon

- First state to allow pharmacists may prescribe and dispense the following contraceptives:
  - 2016: Oral pills and patches
  - 2018: Injectable (including administration)
- OR BOP: created workgroup
  - OR Medical Board
  - OR State Board of Nursing
  - OR Health Authority
  - Subject matter experts
- Challenges:
  - Reimbursement: Recent provider status; created standard with Medicaid to cover pharmacist's assessment at midlevel provider rate
  - Billing: Creating billing software that utilizes medical codes like other providers

Oregon State Board of Pharmacy [http://www.oregon.gov/pharmacy/pages/contraceptiveprescribing.aspx#Law\\_8\\_Rule](http://www.oregon.gov/pharmacy/pages/contraceptiveprescribing.aspx#Law_8_Rule), <https://www.oregon.gov/pharmacy/pages/contraceptiveprescribing.aspx>. Accessed 8/1/18



## California

- 2016: Pharmacists may furnish self-administered hormonal contraceptives
  - Oral, patch, ring, depot
- Age limitations: none specified
- Training: ACPE and BOP approved training program (minimum 1 hour). Graduation ≥2014 from CA pharmacy school with an equivalent curriculum based training program is considered equivalent.
- Documentation in shared electronic medical record and/or via fax to provider
- Challenges:
  - Reimbursement: No reimbursement from insurers yet, but in progress. Not all sites are charging patients a fee.

California State Board of Pharmacy <https://cfsb.com/pharmacy/provider-status/expanding-pharmacist-services/>. Accessed 9/7/18

**HORMONAL CONTRACEPTION SELF-SCREENING TOOL QUESTIONS**

1	What was the first date of your last menstrual period?	/ /	No <input type="checkbox"/>
2a	Have you ever taken birth control pills, or used a birth control patch, ring, or shot/injection? (If no, go to question 3)	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2b	Did you ever experience a bad reaction to using hormonal birth control?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2c	Are you currently using birth control pills, or a birth control patch, ring, or shot/injection?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3	Have you ever been told by a medical professional not to take hormones?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4	Do you smoke cigarettes?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
5	Do you think you might be pregnant now?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
6	Have you given birth within the past 6 weeks?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
7	Are you currently breastfeeding an infant who is less than 1 month of age?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8	Do you have diabetes?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
9	Do you get migraine headaches, or headaches so bad that you feel sick to your stomach, you lose the ability to see, it makes it hard to be in light, or it involves numbness?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
10	Do you have high blood pressure, hypertension, or high cholesterol?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
11	Have you ever had a heart attack or stroke, or been told you had any heart disease?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12	Have you ever had a blood clot in your leg or in your lung?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
13	Have you ever been told by a medical professional that you are at a high risk of developing a blood clot in your leg or in your lung?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
14	Have you had bariatric surgery or stomach reduction surgery?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

## State Rules for Contraceptive Prescribing

	Oregon	California	Colorado	Hawaii	New Mexico	Maryland
<b>Age Requirements</b>	≥18 or <18 with previous Rx	none	≥18	none	none	Regulations and Guidelines due 9/1/18
<b>Products</b>	Oral Patch Depot	Oral Patch Ring Depot	Oral Patch	Oral Patch Ring Depot	Oral Patch Ring Depot	
<b>Training</b>	5 hours \$250	1 hour OR Graduation ≥2014 from CA pharmacy school	4 hours \$250	ACPE and BOP approved program plus CE q 2yrs	4 hour home study then 2 hours live CE q2yrs	
<b>Reimbursement</b>	Medicaid and a few private insurers	None yet	None yet Health profession shortage areas – just passed	None	None	

## Why are we talking about this in Illinois?



### Almost to the finish line!

- Includes language for “pharmacist assessment and consultation” which includes prescribing under a state-wide standing order
- Products proposed: oral, patch, ring (no age restriction)
- Includes language to ensure reimbursement for this service

## Where Can You Buy Contraception Online?

Table adapted from [freebirthpill.org](http://freebirthpill.org). Accessed 8/9/18

Website/App	Age Restrictions	Consultation Fee	Rx Duration	Interaction
heydoctor.co	18-50	\$15	3-6 months	Questionnaire/Chat with MD
lemonaidhealth.com	18+	\$25	12 months	Questionnaire/Video chat in some states
mavenclinic.com	13+; users 13-17 yrs need guardian for 1 <sup>st</sup> virtual visit	\$18-35	Varies	Video chat with provider
nurx.com	12+ (depending on state law); 35+ will be prescribed POP	Free	12 months	Questionnaire
pandiahealth.com (CA only)	Accessible at any age, per CA law	\$39-59	12 months	Questionnaire +/- MD contact
plannedparenthood.org (CA only)	Accessible at any age, per CA law; 35+ can only obtain POP	Free	12 months	Questionnaire
plushcare.com	18+ (<18 need guardian)	Free w/ ins (\$99 w/out)	Not listed	Questionnaire + Video chat
prjkrtruby.com	18+	Free	3-6 months	Questionnaire/Video chat in some states
thepillclub.com	12+	Free	12 months	Questionnaire
virtuwell.com	18-34; EC 18-59	\$49	3-12 months	Questionnaire

## Pharmacist Experiences

## Pharmacist Experiences

### Oregon

#### Implementation:

- Safeway/Albertson's
- Costco
- Rite Aid
- Fred Meyer

#### Reimbursement:

- Recent provider status; created standard with Medicaid to cover pharmacist's assessment at midlevel provider rate

### California

#### Implementation:

- 5%-11% of surveyed pharmacies<sup>1,2</sup>

#### Reimbursement:

- 2013: Provider status legislation passed, but payment for services are not mandated
- No economic incentives

#### Unknown:

- Patient demand
- Pharmacist willingness

1. Batra P, et al. An Evaluation of the Implementation of Pharmacist-Prescribed Hormonal Contraceptives in California. Obstetrics & Gynecology 2018; 131(5):850-855  
2. Gomez AM. Availability of pharmacist-prescribed contraception in California. JAMA 2017;318:2253-4

## Barriers/Solutions

Barrier	Solution
Patient and Provider Perception	-Public relations campaign -Share successful examples
Engaging Pharmacists to Participate	-Pharmacy associations & employers could work together on this initiative -Include content in pharmacy curricula
Payment/Insurer Reimbursement	-Advocate for provider status, which will allow billing mechanisms -Learn about medical claim billing
Pharmacy Workflow	-Corporate support: training, innovation, policy change

## Implications on Practice

- Pharmacists in all 50 states have an opportunity to help patients with contraception
  - Provide guidance: selection, use, and monitoring of contraceptive therapy
  - Pharmacists are encouraged to be proactive as a resource
- U.S. MEC is a useful resource for common questions/problems
  - The MEC provides guidelines for the safety of hormonal contraceptives under a broad range of conditions
- The SPR provides recommendations for managing common contraceptive situations
  - The selection of a contraceptive method includes medical considerations and personal preferences of the patient

**Pharmacists can play an important role in facilitating access to contraception!**

#### **Stay up to date!**

- Pharmacist's Letter®
- Lexicomp®
- APhA
- [Managingcontraception.com](http://Managingcontraception.com)

Which of the following is potentially the largest barrier to pharmacist-prescribed contraception in Illinois?

Reimbursement
Provider acceptance
Workflow implementation
Pharmacist interest

Start the presentation to see live content. Still no live content? Install the app or get help at [Pallix.com/app](https://www.pallix.com/app)

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## Acknowledgements

- Sarah Lynch, PharmD
  - Autumn Stewart-Lynch, PharmD, BCACP, CTTS
  - Krystalyn Weaver, PharmD
  - NASPA
- ELEVATE ILLINOIS COUNCIL OF HEALTH SYSTEM PHARMACISTS 2018 ANNUAL MEETING

Thank you for coming!  
Questions?

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## A Call to Action: Ambulatory Care in Illinois

Brian Cryder, Pharm.D., CACP, BCACP  
 Alexandra Goncharenko, Pharm.D., BCPS  
 Brooke Griffin, Pharm.D., BCACP  
 Mary Ann Kliethermes, BS, Pharm.D., FAPhA  
 Christie Schumacher, Pharm.D., BCPS, BCACP, BC-ADM, CDE  
 Elizabeth Van Dril, Pharm.D., BCPS



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## Ambulatory Care Pharmacy: Current Status in Illinois



Alexandra Goncharenko,  
PharmD BCPS  
 Brian Cryder, PharmD  
 BCACP

The speakers have no conflicts of interest to declare.



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How do you define "ambulatory care pharmacy practice" (ACPP)



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How do you think patients or other health care providers define ACPP



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## Do ACPP have the following responsibilities:

- Ability to prescribe medication and manage disease via CDTM • YES/NO
- Ability to order, interpret and monitor medication related tests • YES/NO
- Monitor response to drug therapy, adverse medication related effects and adherence • YES/NO
- Provide information about the patient's diseases and related medication therapy and offer strategies for improvement • YES/NO



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## Defining Ambulatory Care Pharmacy Practice

- "The provision of **integrated, accessible** healthcare services by pharmacists who are **accountable to addressing medication needs, developing sustained partnerships** with patients, and practicing in the context of family and community"
- "Accomplished through **direct** patient care and **medication management** for ambulatory patients, **long-term relationships, coordination of care, patient advocacy, wellness and health promotion, triage and referral, and patient education and self-management.**"
- "May work in both an **institutional and community-based** clinic involved in **direct** care of a diverse population"



<https://www.bpsweb.org/bps-specialties/ambulatory-care/>



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## Defining Ambulatory Care Pharmacy Practice



- Must attain and maintain appropriate competencies and credentials
- Inter-professional patient care team members
- Specific examples of Scope of Practice/Responsibilities
- Patients should have access to, and have an opportunity to be evaluated by, ambulatory care pharmacists across the continuum of ambulatory care

Am J Health-Syst Pharm. 2014; 71:1390-1



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## Defining Ambulatory Care Pharmacy Practice

- Physician perspective
- Formal consensus statements lacking from medical organizations

POSITION PAPER

### Pharmacist Scope of Practice

American College of Physicians-American Society of Internal Medicine\*

Ann Intern Med. 2002;136(1):79-85.



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## American College of Physicians – American Society of Internal Medicine

- “non-physicians” and “physician extenders”
  - pharmacists, nurse practitioners, and physician assistants
- Described 5 “position statements” both supportive and critical of expansion of the scope of pharmacy practice
- Reimbursement issues
- Liability issues
- Call for research
  - Effects of pharmacist and physician collaboration on physicians’ time with patients
  - Studies examining the outcomes of a community-based pharmacist system

*Ann Intern Med. 2002;136(1):79-85.*

## American Medical Association

- Steps Forward campaign
- Encourage physicians to include a clinical pharmacist and/or a pharmacy technician in their ambulatory care team

Collaborate with pharmacists to improve patient outcomes.  
**Embedding Pharmacists  
Into the Practice**

<https://www.stepsforward.org/modules/embedded-pharmacists>

## Physician Position Statements on Pharmacy Scope of Practice

1. ACP-ASIM supports research into the effects of pharmacy automation and the move to the PharmD degree on pharmacy practice.
  - Moving from prescription provider to pharmaceutical care provider.
  - Collaborative drug therapy – need for pharmacists to access patients, medical records, knowledge and skills, documentation, and compensation.

*Ann Intern Med. 2002;136(1):79-85.*

## Physician Position Statements on Pharmacy Scope of Practice

2. To improve patient safety and reduce medical errors, ACP-ASIM supports physician-directed pharmacist-physician collaborative practice agreements **limited to** pharmacist involvement in patient education and hospital rounds.
3. ACP-ASIM **opposes** independent pharmacists prescriptive privileges and initiation of drug therapy.
  - Little evidence supporting pharmacist prescribing or initiating drug therapy
  - Pharmacists do not have access to complete medical histories
  - Pharmacists do not have the exposure and experience to diagnose and prescribe medications for patients.
  - “Clearly and area that should remain under physician authority.”

*Ann Intern Med. 2002;136(1):79-85.*

## Physician Position Statements on Pharmacy Scope of Practice

4. ACP-ASIM supports the use of the pharmacist as immunization information source, host of immunization sites, and immunizer, as appropriate an allowed by state law.

5. ACP-ASIM reiterates its support of its 1990 therapeutic substitution position. ACPE-ASIM resolves to work with pharmacists in designing therapeutic substitution policies that ensure the highest level of patient care and safety.

Ann Intern Med. 2002;136(1):79-85.



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## How do PATIENTS define ambulatory care pharmacy?

- Supportive of chronic disease management programs as long as pharmacist is trained
  - Lack of awareness of pharmacist training and credentialing
- Pharmacists are easier to access in the community setting
- Expect frequent communication with physician regarding treatment plans
- "Doctors should diagnose and pharmacists should prescribe – they know their drugs, know interactions, so I want their opinion, knowledge."

CMAJ Open 2017



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## How do PAYORS define ambulatory care pharmacy?

- Part D Medication Therapy Management (MTMP) program requirements and information.
- **Requirements for Medication Therapy Management Programs (MTMP):** Under 423.153(d), a Part D sponsor must have established a MTM program that:
  - Ensures optimum therapeutic outcomes for targeted beneficiaries through improved medication use
  - Reduces the risk of adverse events
  - Is developed in cooperation with licensed and practicing pharmacists and physicians
  - Describes the resources and time required to implement the program if using outside personnel and establishes the fees for pharmacists or others
  - May be furnished by pharmacists or other qualified providers
  - May distinguish between services in ambulatory and institutional settings
  - Is coordinated with any care management plan established for a targeted individual under a chronic care improvement program (CCIP)

<https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/MTM.html>



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## Ambulatory Care Pharmacy: Defining our Practice



- ASHP Ambulatory Care Summit (2014)
  - Program designed to advance patient care by building consensus in:
    1. Defining and advancing ambulatory care pharmacy practice
    2. Patient care delivery and integration
    3. Sustainable business models
    4. Outcomes evaluation

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## Ambulatory Care Pharmacy: Current Status in Illinois

- Practice assessment tool created by ASHP to help administrators and practitioners evaluate current practice
- Individualized recommendations provided upon completion of tool
- Data compiled nationally by ASHP



## Ambulatory Care Pharmacy: Current Status in Illinois

- Ability to prescribe medication and manage disease via CDTM
  - RPh: 2 of 5 = yes (nationally 56.9%), Administrator: 7 of 8 = yes (national 64.9%)
- Ability to order, interpret and monitor medication related tests
  - RPh: 4 of 5 = yes (nationally 70.7%), Administrator: 8 of 8 = yes (national 77.7%)

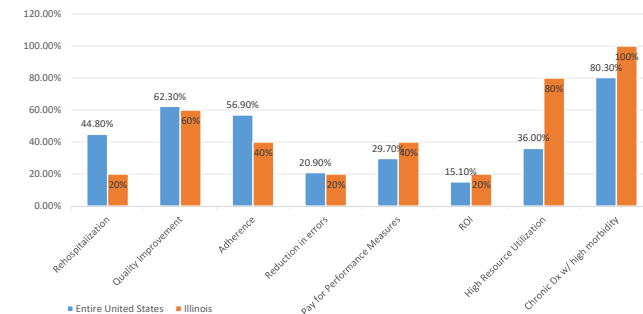
Data from the ASHP Practice Advancement Initiative Assessment  
Ambulatory Care Tool (May 2017)

## Ambulatory Care Pharmacy: Current Status in Illinois

- Monitor response to drug therapy, adverse medication related effects and adherence
  - RPh: 5 of 5 = yes (nationally 92.9%), Administrator: 8 of 8 (national 90.5%)
- Provide information about the patient's diseases and related medication therapy and offer strategies for improvement
  - RPh: 4 of 5 = yes (nationally 91.6%), Administrator: 8 of 8 (national 90.1%)

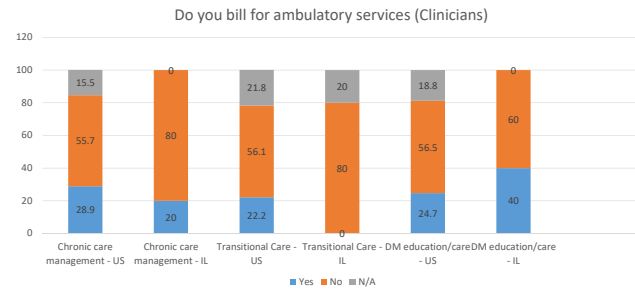
Data from the ASHP Practice Advancement Initiative Assessment  
Ambulatory Care Tool (May 2017)

## Ambulatory Care Pharmacy: Primary Drivers for Pharmacist Care



Data from the ASHP Practice Advancement Initiative Assessment: Ambulatory Care Tool (May 2017)

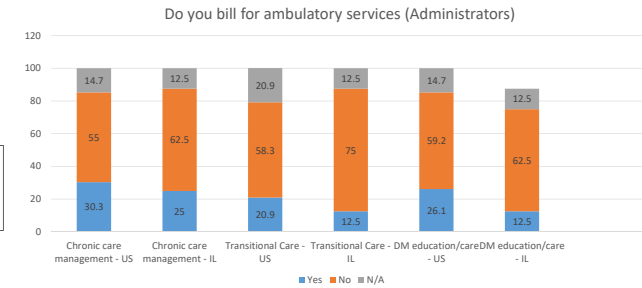
## Ambulatory Care Pharmacy: Billing Practices



Data from the ASHP Practice Advancement Initiative Assessment: Ambulatory Care Tool (May 2017)

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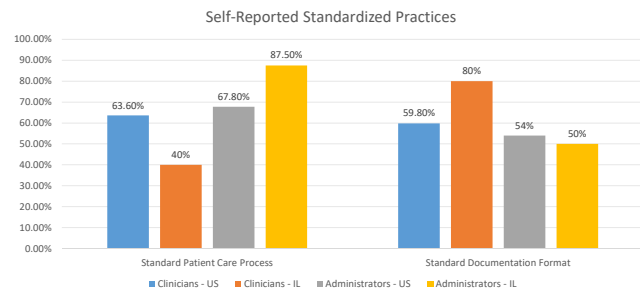
## Ambulatory Care Pharmacy: Billing Practices



Data from the ASHP Practice Advancement Initiative Assessment: Ambulatory Care Tool (May 2017)

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## Ambulatory Care Pharmacy: Standardized Practice



Data from the ASHP Practice Advancement Initiative Assessment: Ambulatory Care Tool (May 2017)

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## Ambulatory Care Pharmacy: Current Status in Illinois

- Given the relatively low respondent numbers in dataset– not dramatically different from national averages in scope of practice, billing or standardization
- However, nationally ambulatory care practice = consistently inconsistent
- Difficult to measure demographic details of ambulatory care pharmacists in Illinois
- Potential current barriers to standardization
  - Limited consistency in exact roles and practices between organizations
  - No delineation of “ambulatory care practice” details in pharmacy practice act
- Where do we go from here?

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## Ambulatory Care Pharmacy: Closing the Gap in Illinois

- Areas to address to align with best practices
  - Move towards universal training and credentialing in ambulatory care pharmacy
  - Consistent practice goals and expectations
  - Improved practices in billing and utilization of cost effective practice
  - Outcomes assessment
  - Increase research and data surrounding benefits of pharmacist involvement
    - Physician time
    - Patient outcomes
    - Cost savings and/or revenue generating?
- More consistent message and increased visibility to patients and other healthcare providers



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## Ambulatory Care Pharmacy: Your Current Practice

- Among the group at your table
  - Have everyone provide a brief summary of your current clinical practice
  - As a group – discuss what are the main differences between the ambulatory care sites
    - Pharmacist responsibilities
    - Common chronic or acute diseases managed
    - Support staff/Resources
    - Billing practices
  - As a group – discuss
    - What elements of your current practices work great
    - What elements would you like to see changed
    - Any current practice changes in progress to improve your clinical practice



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## Challenges and Success on the National Level

Mary Ann Kliethermes, BS, PharmD, FAPhA  
Brooke L. Griffin, PharmD, BCACP

The speakers have no conflicts of interest to disclose.



Unless otherwise stated, images obtained from <https://pixabay.com/>  
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## Learning Objective - Pharmacist

- Interpret, from a national perspective, current health care challenges and sustainable opportunities for pharmacists in ambulatory care settings.



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Can you explain what you do to your parents?

- A. I struggle
- B. I easily can



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Which term do you believe best describes pharmacist patient care services?

- A. CMM
- B. MTM
- C. Medication Optimization
- D. Medication Management Services



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Is Ambulatory Pharmacy Patient Care Services Heading to a Perfect Storm

Terminology Issues

Medication  
Management Services

Pharmaceutical Care

Wicked Challenges for  
Ambulatory  
Pharmacy Practice

Are all pharmacists alike?



What is it we do?  
What is our philosophy  
care

Roles  
Accountability  
Responsibility



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### Listening to what others are saying...

- How do I find a pharmacist that will meet my needs? How do I find a pharmacist like you? *Medical Director of a Physician Group*
- "I fought to get a pharmacist, but the ones we have are not like the ones I trained with?" *Physician Board member of a large health-system*
- What is the intervention? There's definitely a need for it, but I need to know what I'm buying." *CMO of National Insurer*
- "We need consistency in the practice of CMM. Unless we train them, we are unsure whether they truly know what CMM is." *Director of CMM in a large integrated health system*



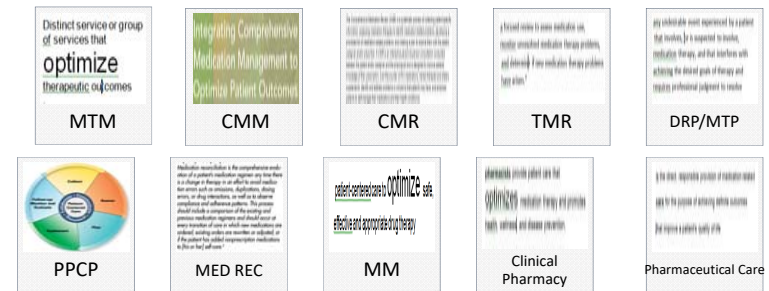
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## Terminology: Words Used in Pharmacy Literature to Describe Patient Care Services

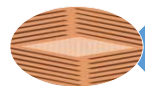


Courtesy of Dr. Patrick Clay and his student

## Alphabet Terminology Soup



## Why is terminology important?



Users of our services understanding and perceptions



Attribution of value



Developing evidence base for value

## Raising this issue to (inter)national discussion

Vol 3 Clin Pharm (2016) 30:200-213  
DOI 10.1007/s13254-016-0204-9

COMMENTARY

Terminology, the importance of defining

J. W. Figger van Mül · Martin Thomas<sup>a</sup>

Harmonization of Terms for Clinical Pharmacy: If It Walks Like a Duck...

BY JERRY BAUMAN

UIC alumni publication 2016

Terminology Is Important Written by Daniel Aistrope, Pharm.D., BCACP Director, Clinical Practice Advancement ACCP Report 7 2016

"Despite pharmacists confirming that they are engaged in CMM and despite the existence of several guideline documents, standards of practice, and definitions of CMM in the literature, a consistent approach to CMM is lacking." ACCP CMM project

CheckMark

SCIENCE AND PRACTICE

Journal of the American Pharmacists Association

Commentary

Journal of the American Pharmacists Association

Commentary

A consistent professional brand for pharmacy—the need and a path forward

Martine A. Spentice, Lorenz G. Anderson<sup>a</sup>

Get the medications—and the name-- right: Comprehensive Medication Management by Katherine H. apps, president, Health2 Resources blog

## Where Are Other Countries

### Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes

NICE guideline [NG5] Published date: March 2015 [Uptake of this guidance](#)

#### Medication Management

Medication management involves patient-centred care to optimize safe, effective and appropriate drug therapy. Care is provided through collaboration with patients and their health care teams.

Canadian Pharmacist Association\*



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## Medication Management Services

Spectrum of patient-centered, pharmacist-provided, collaborative services that focus on medication appropriateness, effectiveness, safety and adherence with the goal of improving health outcomes.

JCPP press release: <https://naspa.us/wp-content/uploads/2018/03/Press-release-MMS-2018-1.pdf>



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## Are we all alike?

Agree on an axiom:  
Pharmacists and Patients are different



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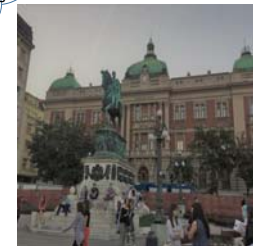
## Flaws with all being the same

Penguins are black and white  
Some old TV shows are black and white. Therefore, some penguins are old TV shows



Are the assumptions correct and more importantly safe?

Does it stifle or discourage innovation?  
Is it wise use of resources?



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## 11

## Pharmacist Services through a Population Health Lens?

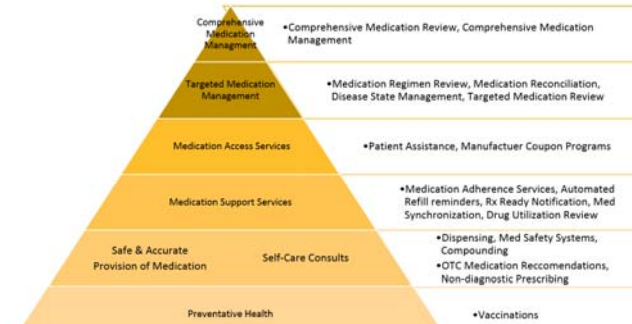


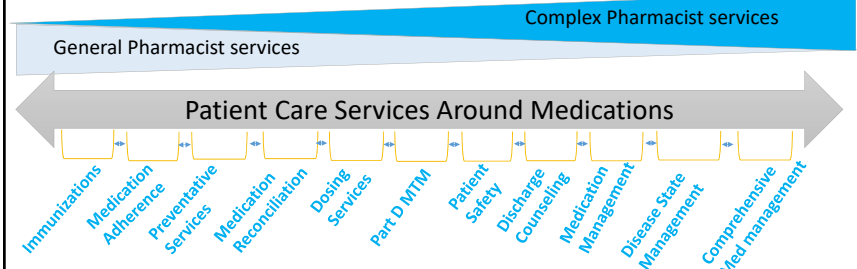
Figure 1. Optimization of Health through Pharmacist Provided Services

Image Credit: HAIMM, MN Health System Collaborative. Reprinted with permission

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## Medication Management services

Patients and their needs: intensity and complexity



Required for each bucket: highly reliable standard services provided in a consistent and standard way to produce consistent and expected outcomes.

Pharmacist Patient Care Process

## Defining the Services

What are the discrete services and the range of services?

Where and how do they fit on the continuum?

What are standard, consistent elements of each discrete service?

What skills, knowledge and credentials are desirable for a provider performing the services in each bundle of discrete services?

## Successful Ambulatory Care Practices in Other States

In states with successful ambulatory care practices, which of the following is the greatest contributor?

- A. Designation as a legal health care provider
- B. Optimized pharmacy practice for scope of practice
- C. Payment for services in State Insurance Code
- D. Governmental Advocacy
- E. Physician Champions



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## Successful Ambulatory Care Practices in Other States

Why Successful?

Why Sustainable?

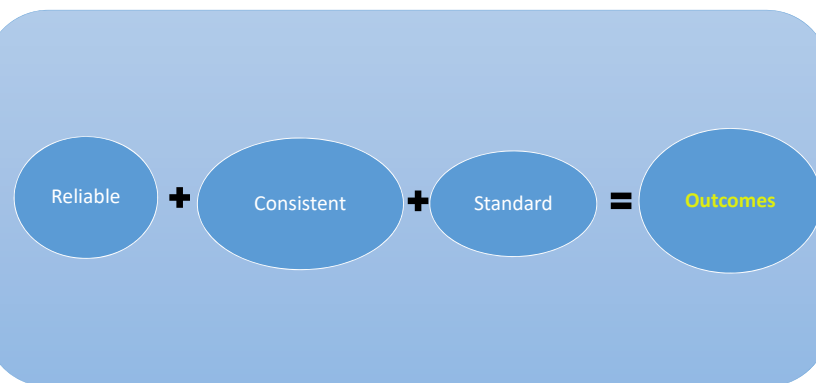
What are the Opportunities?

What have they Defined?



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## Quality of Services



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## Documented Support

### American Medical Association

- Embedding Pharmacists Into the Practice
- <https://www.stepsforward.org/modules/embedded-pharmacists>

### Report to the US Surgeon General

- Giberson S, Yoder S, Lee MP. *Improving Patient and Health System Outcomes through Advanced Pharmacy Practice. A Report to the U.S. Surgeon General.* Office of the Chief Pharmacist. U.S. Public Health Service. Dec 2011.

### CDC

- Partnering with Pharmacists in the Prevention and Control of Chronic Diseases
- [https://www.cdc.gov/dhdsr/programs/spha/docs/pharmacist\\_guide.pdf](https://www.cdc.gov/dhdsr/programs/spha/docs/pharmacist_guide.pdf)

### American Academy of Family Physicians

- "The AAFP supports arrangements where the pharmacist is part of an integrated, team-based approach to care. The AAFP believes that independent prescription authority for pharmacists will further fragment the American health care system and will undermine the national goals of integrated, accountable care and models such as the PCMH." <https://www.aafp.org/about/policies/all/pharmacists.html>



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## Pharmacist Contributions in the Literature<sup>1</sup>

### MDs can see more patients

Nichol A. Downs G. The pharmacist as physician extender in family medicine office practice. J Am Pharm Assoc. 2006;46:77-83.

### Reduce Hospitalizations

In patients with DM or HF<sup>4</sup>

### Improve Outcomes for Various Disease States

Geisinger Health System: Providing a One-Stop Shop for Medication Management." AHIP Innovations in Medication Therapy Management

APHA Document [https://cdn.ymaws.com/www.chronicdisease.org/resource/resmgr/cvh/pharm\\_&\\_hc\\_puzzle.pdf](https://cdn.ymaws.com/www.chronicdisease.org/resource/resmgr/cvh/pharm_&_hc_puzzle.pdf)

### Prove ROI

Reducing total annual health expenditures exceeded the cost of providing MTM services by more than 12 to 1<sup>2</sup>

Significant reduction in per member per month cost and controlled spending growth overall<sup>3</sup>

1. The Patient-Centered Medical Home: Integrating Comprehensive Medication Management to Optimize Patient Outcomes. BSCSOURCE GUIDE. <https://www.bscsource.org/sites/default/files/media/medmanagement.pdf>. Accessed 7/5/18
2. Iseltts BJ, Schondelmeyer SW, Artz MB, Lenarz LA, et al. Clinical and economic outcomes of medication therapy management services: The Minnesota experience. J Am Pharm Assoc. 2008;48:203-211
3. Iseltts, Brummet, Ramalho de Oliveira, Moen-Medical Care-Nov 2012
4. Viswanathan et al. JAMA Intern Med. 2015;175(1):76-87.

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## Someone Should Write a Meta-Analysis!

### Two teams tried...

#### 1. Pharmacists' Effect as Team Members on Patient Care: Systematic Review and Meta-Analyses

- Reviewed 298 articles
- Ambulatory, community and inpatient teams
- Small number of pharmacists in some studies
- Majority did not report power or sample size analyses
- Pharmacist activities varied so greatly that it was challenging to associate interventions with outcomes

#### 2. Medication Therapy Management Interventions in Outpatient Settings: A Systematic Review and Meta-analysis

- Reviewed 44 articles
- "evidence was insufficient to determine the effect of MTM interventions on most evaluated outcomes (eg, drug therapy problems, adverse drug events, disease-specific morbidity, disease-specific or all-cause mortality, and harms)."
- Authors stated there was "inconsistency and imprecision" that stem in part from underlying heterogeneity in populations and interventions."

1. Chisholm-Burns MA, et al. US Pharmacists' Effect as Team Members on Patient Care: Systematic Review and Meta-Analyses. Medical Care, Vol. 48, No. 10 (October 2010), pp. 923-933
2. Viswanathan et al. JAMA Intern Med. 2015;175(1):76-87.

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## Unanswered Questions

Gaps in Practice, therefore gaps in the literature:

- Standardization in practice
- Definition of the pharmacists' role
- Difference in professional credentials and experience
- Difference in resources and funding
- Undefined value

Jorgenson et al. International Journal of Pharmacy Practice 2014, 22, pp. 292-299

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What can we do in Illinois?  
Which states have successful Ambulatory Care models?

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## Washington: History



- 1979 CPA in Pharmacy Practice Act
- 1993 Health Services Act – includes compensation for “every category of provider”
- 1994-2012 - numerous attempts for pharmacist compensation
  - Insurers stated they were in compliance by paying professional dispensing fees
- 2013 Attorney General informal opinion that pharmacists are health care providers and must be compensated
- 2015 – SB 5557 – pharmacists as medical providers requiring compensation under major medical insurance for pharmacists providing health services contained in benefits

## Washington: Getting There

### 2000's

2 pharmacists published results:

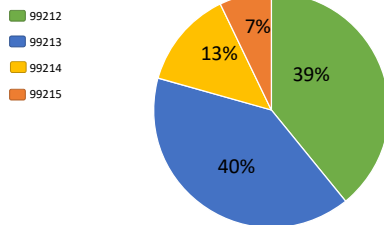
- Lowered per member per month drug costs (use of generics and OTCs)
- Increase of 15% of patients with controlled BP
- Avoided \$450,000 in hospital costs by initiating an outpatient DVT program

Devine EB et al. Strategies to optimize medication use in the physician group practice: the role of the clinical pharmacist. J Am Pharm Assoc. 2009;49:181-91.

## Washington: Currently

### Productivity Review YTD August data

Breakdown of CPT codes used per visit



CPT Code	Visit Volume
99212	11,120
99213	11,436
99214	3,832
99215	2,032

**\*\* Does not include linked visits or shared medical appointments**

Permission courtesy of Amanda Locke, Virginia Mason

## Washington: Currently

- Patient financial services available
- Marketing tools to educate patients on pharmacist role



Permission courtesy of Amanda Locke, Virginia Mason

## Minnesota: History



### Pharmacy Practice Act

- (1) interpretation and evaluation of prescription drug orders;
- (2) compounding, labeling, and dispensing drugs and devices (except labeling by a manufacturer or packager of nonprescription drugs or commercially packaged legend drugs and devices);
- (3) participation in clinical interpretations and monitoring of drug therapy for assurance of safe and effective use of drugs, including the performance of laboratory tests that are waived under the federal Clinical Laboratory Improvement Act of 1988, United States Code, title 42, section 263a et seq., provided that a pharmacist may interpret the results of laboratory tests but may modify drug therapy only pursuant to a protocol or collaborative practice agreement;
- (4) participation in drug and therapeutic device selection; drug administration for first dosage and medical emergencies; drug regimen reviews; and drug or drug-related research;
- (5) participation in administration of influenza vaccines to all eligible individuals six years of age and older and all other vaccines to patients 13 years of age and older by written protocol with a physician licensed under chapter 147, a physician assistant licensed under chapter 147A, or an advanced practice nurse authorized to prescribe, dispense, and administer under chapter 147A, or advanced practice nurses authorized to prescribe, dispense, and administer under section 148.235. Any changes in drug therapy made pursuant to a protocol or collaborative practice agreement must be documented by the pharmacist in the patient's medical record or reported by the pharmacist to a practitioner responsible for the patient's care;
- (6) participation in the initiation, management, modification, and discontinuation of drug therapy according to a written protocol or collaborative practice agreement between: (i) one or more pharmacists and one or more dentists, optometrists, physicians, podiatrists, or veterinarians; or (ii) one or more pharmacists and one or more physician assistants authorized to prescribe, dispense, and administer under chapter 147A, or advanced practice nurses authorized to prescribe, dispense, and administer under section 148.235. Any changes in drug therapy made pursuant to a protocol or collaborative practice agreement must be documented by the pharmacist in the patient's medical record or reported by the pharmacist to a practitioner responsible for the patient's care;
- (7) participation in the storage of drugs and the maintenance of records;
- (8) patient counseling on therapeutic values, content, hazards, and uses of drugs and devices;
- (9) offering or performing those acts, services, operations, or transactions necessary in the conduct, operation, management, and control of a pharmacy; and
- (10) participation in the initiation, management, modification, and discontinuation of therapy with opiate antagonists, as defined in section 604A.04, subdivision 1, pursuant to: (i) a written protocol as allowed under clause (6); or (ii) a written protocol with a community health board medical consultant or a practitioner designated by the commissioner of health, as allowed under section 151.37, subdivision

## Minnesota: Getting There

### Fairview Example

- 1997: Introduced CMM approach
- Included:
  - collaborative practice agreements
  - coordination with expanded care teams
  - utilization of patient data to ensure economic and clinical outcomes are identified and met
- Helped ACOs meet quality and financial benchmarks

2005: Coverage of pharmacist MTM (CMM-level) services for Medicaid and state employee health programs with positive results; the state has expanded eligibility to more patients

### Park Nicollet Example

- 11 Pharmacist Providers at 15 Ambulatory Clinic sites, 1 PGY1 Resident, 1 Patient Outreach Coordinator, and 1 FTE Pharmacist Leader
- 2017 Med Management Data
  - >5k Patients, >9k Encounters
  - >13k Med Related Problems (76% Resolved)

Brummel A, Lustig A, Westrich K. "Best practices: improving patient outcomes and costs in an ACO through comprehensive medication therapy management." J Managed Care Specialty Pharm. 2014;20(12):1152-1158

## Minnesota: Currently



### ACO ESRD Costs- Patients with a MTM Visit in 2016

ACO members utilizing pharmacists:	2016 Five months experience	Part A Medicare Costs Per Patient Per Month	Part B Medicare Costs Per Patient Per Month	Admits per 1,000	ER Visits per 1,000
No	ESRD Control (24)	\$ 34,705	\$ 3,998	1,083 (26 admits)	1,292 (31 ER Visits)
Yes	MTM ESRD (17)	\$21,770	\$3,144	353 (6 admits)	1,000 (17 ED Visits)
	Difference between Control and MTM Intervention	\$12,935	\$854	20	14

Slide used with permission from Molly Ekstrand, BPharm, BCACP, AE-C, Park Nicollet Health Services;  
 "The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document."

## South Carolina: Physician Productivity

Provider	2013 Payment/ Work Day	2014 Payment/ Work Day	% Increase Payment/ Work Day	2013 Q2 Visits/Day	2014 Q2 Visits/Day	% Total Referrals to PharmD
MDA	\$2,741	\$3,499	27.7%	24.2	25.0	46%
MDB	\$3,100	\$3,701	19.4%	31.1	31.2	9%
MDD	\$2,602	\$3,385	30.1%	23.5	23.7	27%
MDT	\$2,582	\$3,000	16.2%	23.5	24.8	11%
MDV	\$2,878	\$3,177	10.4%	24.0	22.7	7%
AVERAGE	\$2,781	\$3,352	20.6%	25.3	25.5	100%

### Contributing Factors:

- Fee Increase November 2013
- More New Patient Visits
- More Complex Visits

Original Research Kennedy Pharmacy Innovation Center

Permission courtesy of Bob Davis, The Kennedy Center

## Other States

### California<sup>1</sup>

- 2014: SB 493 declared pharmacists to be health care providers who have the authority to provide health care services
- AB 2084: if enacted, would allow for provision of CMM services for certain high-risk Medicaid patients

### Tennessee<sup>2</sup>

- 2017: Pharmacists as Providers" ([HB 405/SB 461](#)) gives Tennessee pharmacists formal recognition as providers through managed health insurance issuers, including reimbursement and inclusion in medical networks, as providers of care

### North Carolina<sup>3,4</sup>

- 2000: Clinical Pharmacist Practitioner (CPP) Act, authorizes CPPs to implement drug therapies as outlined by a CPA
- 2013: NC Chronic Care Act, includes provisions for CMM for certain publicly funded beneficiaries

1. [http://www.leginfo.ca.gov/pub/15-16/bill\\_asm/ab\\_2051-2100/ab\\_2084\\_bill\\_20150217\\_introduced.htm](http://www.leginfo.ca.gov/pub/15-16/bill_asm/ab_2051-2100/ab_2084_bill_20150217_introduced.htm)  
 2. <https://www.pharmacist.com/article/new-tennessee-law-formally-recognizes-pharmacists-providers>  
 3. [GetTheMedicationsRights.v22final-5.20](#)  
 4. NC Chronic Care Coordination Act <http://www.ncleg.net/Sessions/2013/Bills/House/PDF/H459v3.pdf>



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In states with successful ambulatory care practices, which of the following is the greatest contributor?

- A. Designation as a legal health care provider
- B. Optimized pharmacy practice for scope of practice
- C. Payment for services in State Insurance Code
- D. Governmental Advocacy
- E. Physician Champions



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## Discussion



- What elements can we take from other successful states?
- What is the first thing we should tackle in Illinois?

<https://pixabay.com/en/group-team-feedback-confirming-1825510/>



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## Acknowledgements and Additional Contact Information

- Park Nicollet
  - Kristen.Kopski@parknicollet.com
  - Park Nicollet Health Services ACO website
  - <http://www.parknicollet.com/About/accountable-care-organization>
  - Gena.Graves@parknicollet.com
- Centers for Medicare & Medicaid Services
  - Questions regarding the Next Generation ACO Model can be directed to CMS  
[NextGenerationACOModel@cms.hhs.gov](mailto:NextGenerationACOModel@cms.hhs.gov)



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## Ambulatory Care Clinical Pharmacists Role in Value-Based Payment Models

Christie Schumacher, PharmD, BCPS, BCACP, BC-ADM, CDE  
Associate Professor, Pharmacy Practice  
Midwestern University Chicago College of Pharmacy  
Advocate Medical Group – Southeast Center

Liz Van Dril, PharmD, BCPS  
Clinical Assistant Professor, Pharmacy Practice  
University of Illinois – Chicago  
Clinical Pharmacist, Ambulatory Pharmacy Services – Internal Medicine



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## Disclosure

Drs. Christie Schumacher and Liz Van Dril have no actual or potential conflicts of interest in relation to this activity



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## Learning Objective - Pharmacist

Evaluate the impact of ambulatory care clinical pharmacists on clinical and economic outcomes in value-based payment models.



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What services are you  
interested in providing at your  
site?



What outcomes are you measuring to demonstrate benefit?

What implementation challenges have you encountered?

What sustainability challenges have you encountered?

### Advocate Medical Group Southeast Center

Advocate Health Care's ACO is one of the largest in the country

Over 250 clinic locations in the Chicago metropolitan area



ACO = Accountable Care Organization



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## Payer Mix

Medicare Advantage Full Risk	59%
Medicare Shared Savings Program	19.4%
Commercial Full Risk	11.3%
Commercial FFS	8%
Medicaid	1.8%
Self-Pay	0.4%

FFS = fee-for-service



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## Outcomes-Based Reimbursement Model

### Capitated Reimbursement

- Medicare Advantage and Commercial Full Risk
  - Incentive for keeping the patient well
- Medicare Shared Savings Program

### Incentive to focus on preventative health care

- Meet performance measures
- Prevent hospitalizations
- Decrease cost



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## Outcomes-Based Reimbursement Model

### Breeds team-based model of care

- Utilize clinical pharmacist for:
  - More frequent follow-up
  - Timely medication titration
  - Improvement in performance measures



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## Outcomes-Based Reimbursement Model

### 99211

- Internal tracking tool to measure number of individual visits

### 90036

- Patients seen the same day as their physician
- "No charge" office visit



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## Identifying the Need

### Heart failure (HF) transitions of care

313

- Number of patients hospitalized for HF exacerbation (HHF) in 2008 that were readmitted within 30 days for a subsequent HHF

\$2.4 million

- Estimated risk cost for 30-day readmissions for HHF

36%

- Percentage of these patients that had a repeat HHF in the one-year period following readmission for HHF



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## Clinical Pharmacist Services

### Initially designed as HF clinic

- Decrease hospitalizations
- Initiate and optimize GDMT for HF
- Improve medication adherence
- Reduce medication costs for patients

### Expanded collaborative care

- Diabetes
- Hypertension
- Hyperlipidemia
- Asthma
- COPD
- Post-hospital follow-ups



All Internal Medicine  
Chronic Disease  
States

GDMT = guideline-directed medication therapy



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## Clinical Pharmacist Services

### Collaborative Practice / Practice by Protocol

- Develop and implement an individualized patient care plan
- Initiate, discontinue and titrate medications
- Provide medication reconciliation and education to improve adherence
- Order and interpret laboratory values
- Monitor safety and efficacy
- Identify barriers to adherence
- Arrange appropriate medical referrals

### Educate

- Patients, physicians, medical staff, pharmacy students and residents



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## Clinical Pharmacist Services

8 to 16 patients  
scheduled daily

- Initial visits and post-hospital follow-ups: 60 minutes
- Follow-up visits: 30 minutes
- Utilize students and residents

Visit type

- Face-to-face independent
- Shared visits with physician

Available at any  
time for physician  
consults

- Establish care during physician visit to improve visit adherence with PharmD visits

Communication

- Electronic medical record
- Shared office space

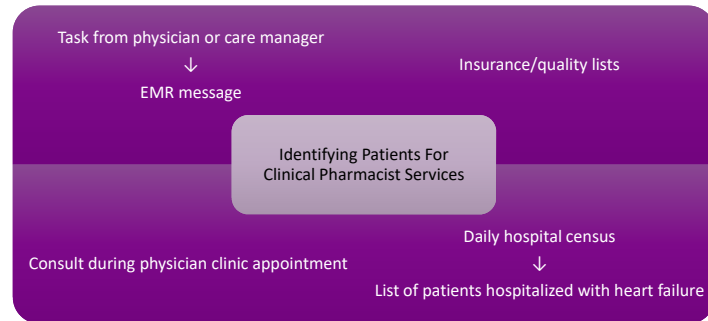
Limited availability  
due to demand

- ~5-15 new referrals each week



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## Referral Process



## Pilot Program Data from Clinical Pharmacist-Managed Patients with Heart Failure

### Patients with HF managed by Clinical Pharmacist, November 2009– August 2010 (n = 111)

Inpatient admissions in the 10 months pre-PCMH implementation	63 (57%)
Inpatient admissions in the 10 months post-PCMH implementation	30 (27%)
Average Cost per HF admission	\$8,500
Potential Cost Avoidance for patients based on pre/post-PCMH implementation	\$280,000

HF = heart failure; PCMH = patient-centered medical home

## Pilot Program Data from Clinical Pharmacist-Managed Patients with Diabetes

### Patients with DM managed by Clinical Pharmacist, May 2010 – November 2011 (n = 153)

	Baseline	Study Period Conclusion	Change
Average A1c (%)	9.2 (±2.6)	7.7 (±1.7)	-1.5
Patients with A1c < 7% <sup>a</sup>	25 (16%)	49 (32%)	24 (16%)
Average LDL (mg/dL)	97 (±30.6)	81 (±25.6)	-16
Patients with LDL < 100 mg/dL	81 (53%)	103 (67%)	22 (14%)
Average SBP (mmHg)	143 (±22.1)	129 (±17.9)	-14
Average DBP (mmHg)	77 (±10.6)	70 (±10.8)	- 7
Patients taking ACEI or ARB	110 (72%)	133 (87%)	23 (15%)
Patients taking statin	92 (60%)	121 (79%)	29 (19%)

<sup>a</sup>Before American Diabetes Association guidelines created less stringent, individualized goals

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; DM = diabetes mellitus; LDL = low-density lipoprotein; SBP = systolic blood pressure

## AMG-SE Quality Metrics Dashboard

DM Management, aged ≥ 65 years	2009 Results (%) <sup>a</sup>	2013 Results (%)	2014 Results (%)
Annual Eye Exam	35	71	75
Annual Foot Exam	71	86	84
A1c Performed	80	93	96
A1c < 8%	32	84	80
A1c > 9%	41	9	11
LDL Performed	78	94	93
LDL < 100 mg/dL	40	63	65
LDL > 130 mg/dL	39	19	16
HTN Control (< 140/90 mmHg)	62	91	91
Nephropathy Testing	85	98	100

<sup>a</sup>Before the clinical pharmacist managed patients at the center

AMG-SE = Advocate Medical Group Southeast Center; DM = diabetes mellitus; LDL = low-density lipoprotein; HTN = hypertension

## AMG-SE Quality Metrics Dashboard

Generic Medication Use	2009 Results (%) <sup>a</sup>	2013 Results (%)	2014 Results (%)
Generic medication use	80	92	92
Generic statin use	75	96	96
Heart Failure Management	2009 Results (%) <sup>a</sup>	2013 Results (%)	2014 Results (%)
Appropriate medication: ACEI or ARB	74	88	95
Appropriate medication: BB	82	80	83

<sup>a</sup>Before the clinical pharmacist managed patients at the center  
ACEI = angiotensin-converting enzyme inhibitor; AMG-SE = Advocate Medical Group Southeast Center; ARB = angiotensin receptor blocker; BB = beta-blocker; HF = heart failure

## Implementation Challenges

### Gaining physician support

- In-services at physician meetings
- Coordination with physician schedules

### Workflow inconsistencies at different centers

- Shared visits
- Physicians' needs
- Collaborative practice limitations

## Sustainability Challenges

### Workload

- Challenging to sustain with growth and demand

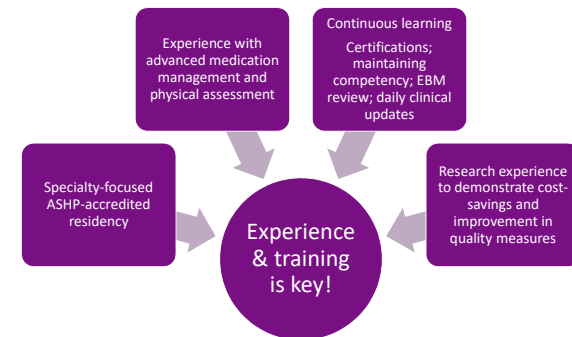
### Team expansion and cross coverage

- Variability in skill sets among team members
- Maximize skill sets based on training
- Communication with patients and health care team

### Shared faculty member

- Multiple responsibilities
- Same accountability as full-time employees

## Professional Development



## Questions and Discussion

What services are you interested in providing at your site?

What outcomes are you going to measure (or measuring) to demonstrate benefit?

What implementation challenges have you encountered?

What sustainability challenges have you encountered?

## **Worksheet**

### **Ambulatory Care Pharmacy: Your Current Practice**

Among the group at your table:

1. Have everyone provide a brief summary of your current clinical practice

2. As a group – discuss the main differences between the ambulatory care sites

- Pharmacist responsibilities
- Common chronic or acute diseases managed
- Support staff/Resources
- Billing practices

3. As a group – discuss

- What elements of your current practices work great
- What elements would you like to see changed
- Any current practice changes in progress to improve your clinical practice

## Quality Improvement Pearls

Stephanie Beam, Pharm.D., BCOP  
 Julie Downen, Pharm.D., BCPS, CLSSBB  
 Jordan Johnson, Pharm.D.  
 Ashlie Kallal, Pharm.D., CLSSBB



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## Reducing Hazardous Drug Exposure

Stephanie Beam, PharmD, BCOP  
 Rush Copley Medical Center

Speaker has no conflicts of interest to disclose



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### Learning Objective - Pharmacist and Technician

- Define Hazardous Drug and list consequences of exposure



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### Background

- 1970's: Chemotherapy agents were found to be linked to secondary cancers
- 1980's: OSHA recommended the use of Biological Safety Cabinets
- 1990: ASHP published a document on handling cytotoxic and hazardous drugs
- 1995: OSHA issues new guidelines on controlling occupational exposure to hazardous drugs
- 2004: NIOSH alert issued - Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings
- USP 800: Guidelines to protect healthcare workers from hazardous drug exposure – implementation in December 2019.



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## Why are things changing?

- According to CDC, approximately 8 million US health care workers are exposed to Hazardous Drug's (HD) each year
- HD's have been known to cause:
  - Teratogenicity
  - Reproductive toxicity
  - Organ toxicity
  - Carcinogenicity
- Purpose of USP 800 is to provide standardized guidelines when handling HD's that help reduce unnecessary exposure

NIOSH 2014. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2014. By Connor TH, Mackenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH US DHHS, CDC



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## Consequences of hazardous drug exposure

- Routes of Exposure:
  - Absorption: Skin contact / handling contaminated materials
  - Inhalation: Crushing pills, mixing liquids
  - Ingestion: Hand to mouth contact / handling food with contaminated hands
- Short-term effects of exposure:
  - Skin irritation / burning
  - Ocular irritation
  - Flu-like symptoms
  - GI toxicity
- Long-term effects of exposure:
  - Birth defects
  - Fertility impairment
  - Secondary cancers

ASHP. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006;63:1172-1193.

NIOSH 2014. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2014. By Connor TH, Mackenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH US DHHS, CDC



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## Are you currently using a Closed System transfer device (CSTD) at your institution?

- Yes – only for chemotherapy administration
- Yes – only for chemotherapy compounding
- Yes – for both chemotherapy administration and compounding
- No - currently not using a CSTD



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## USP 800 recommendations for CSTD use

- A CSTD must not be used as a substitute for a C-PEC when compounding
- CSTDs **should** be used when compounding HDs when the dosage form allows
- CSTDs **must** be used when administering antineoplastic HDs when the dosage form allows

C-PEC = containment primary engineering control = ventilated device designed to minimize worker and environmental HD exposure when directly handling HDs  
US Pharmacopeial Convention. General Chapter <800> Hazardous drugs – handling in healthcare settings. 2016.



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## USP 800 recommendations - CSTD evaluation

- Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies and demonstrated containment reduction

National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. A performance test protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs (draft). [www.cdc.gov/niosh/topics/hazdrugs/pdfs/performance-test-protocol-closed-system-transfer-devices.pdf](http://www.cdc.gov/niosh/topics/hazdrugs/pdfs/performance-test-protocol-closed-system-transfer-devices.pdf), 2017

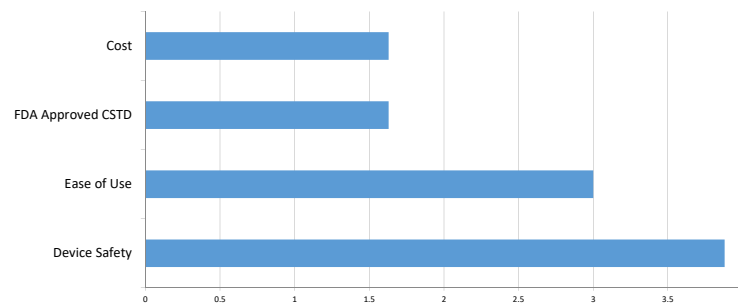
US Pharmacopoeial Convention. General Chapter <800> Hazardous drugs – handling in healthcare settings. 2016:285.

## CSTD Failure



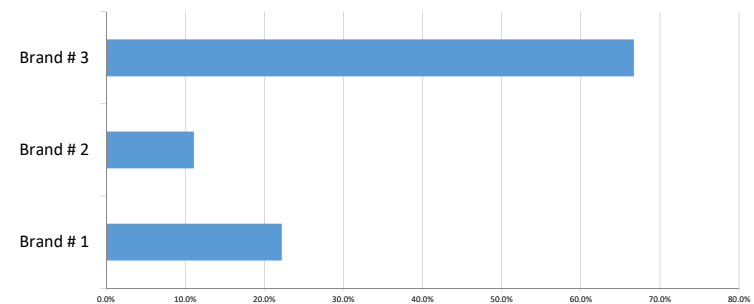
## CSTD Survey – Ranking By Level of Importance

Pharmacy and Nursing

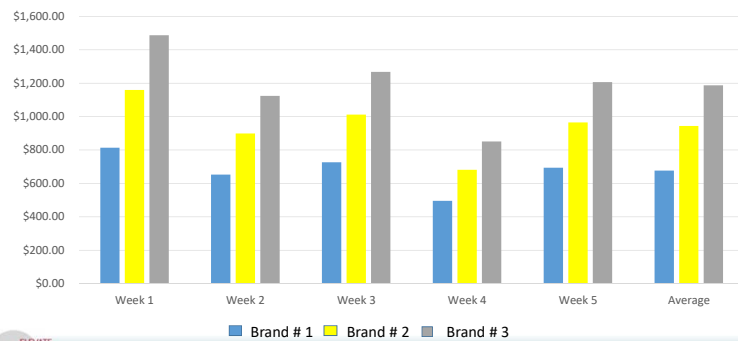


## CSTD Survey – Which CSTD would you prefer

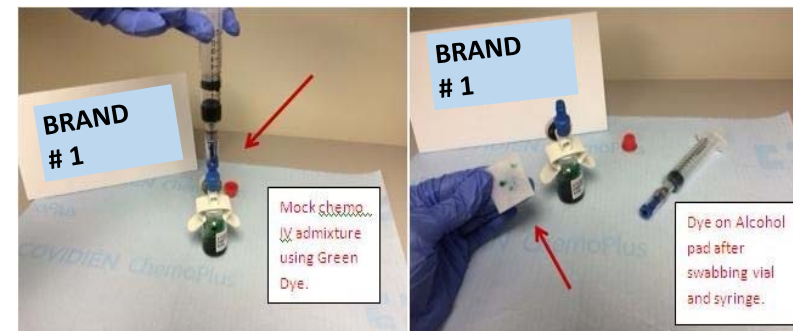
Pharmacy and Nursing



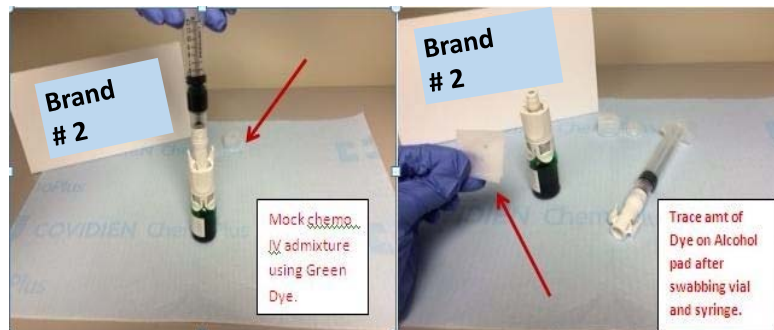
## Cost Comparison – weekly average



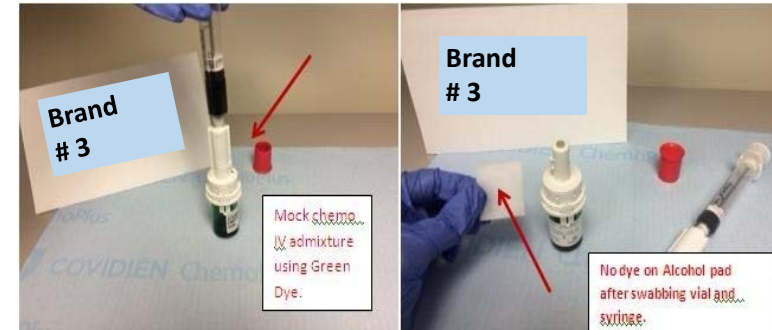
## CSTD evaluation



## CSTD evaluation



## CSTD evaluation



## Selecting a CSTD

- Does the CSTD meet the definition of a closed system - mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system
- Does the CSTD have FDA 510(k) clearance
- Is the CSTD compatible with other administration equipment
- Safety
- Ease of Use
- Cost



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## Conclusion

- Lack of a universal performance standard for evaluating CSTDs
- NIOSH is currently developing performance protocols that may be useful for evaluating CSTDs
- Pharmacists and other health care professionals should evaluate all available information to make decisions to protect the health of those individuals who prepare, handle and administer hazardous drugs

US Pharmacopeial Convention. General Chapter <800> Hazardous drugs – handling in healthcare settings. 2016.



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## References

- NIOSH 2014. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2014. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH US DHHS, CDC.
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- US Pharmacopeial Convention. General Chapter <800> Hazardous drugs – handling in healthcare settings. 2016.
- National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. A performance test protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs (draft). [www.cdc.gov/niosh/topics/hazdrugs/pdfs/performanceprotocolclosedsystemtransferdevices.pdf](http://www.cdc.gov/niosh/topics/hazdrugs/pdfs/performanceprotocolclosedsystemtransferdevices.pdf). 2017.



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## Utilizing EHR Tools to Improve IV to PO Conversion

Julie Downen, PharmD, BCPS  
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## Disclosures

I have no financial relationships to disclose regarding the topic of this presentation



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## Learning Objective – Pharmacist and Technician

Describe strategies that can be implemented into the EHR to assist with IV to PO conversion.



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## Background

Conversion of intravenous (IV) medications to oral (PO):

- Reduces costs
- Reduces length of stays
- Improves patient comfort and ambulation
- Reduces risk of infusion related reactions
- Reduces risk for infections associated with IV catheters

Barlam TF, Cosgrove SE, Abbo LM. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology. Clin Infect Dis. 2016;62(10):e151-e177.  
Kuper K. Intravenous to Oral Therapy Conversion. In: Mordough L. Competence Assessment Tools for Health-System Pharmacists. 4<sup>th</sup> ed. American Society of Health-System Pharmacists; 2008. 347-360.



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## Memorial Medical Center

- 500 bed Magnet designated, teaching-community hospital
- Bariatric Center of Excellence
- Kidney-Pancreas Transplant Center
- Regional Cancer Center
- Level I Trauma Center
- Regional Burn Center
- Comprehensive Stroke Center



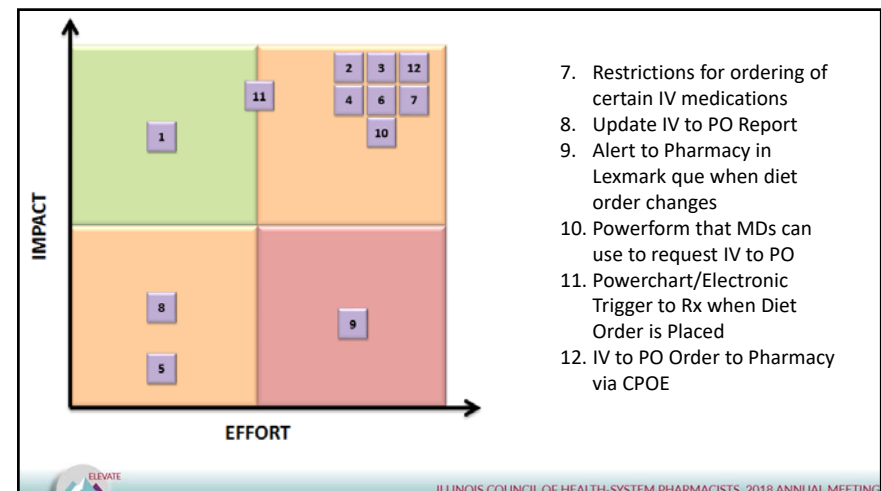
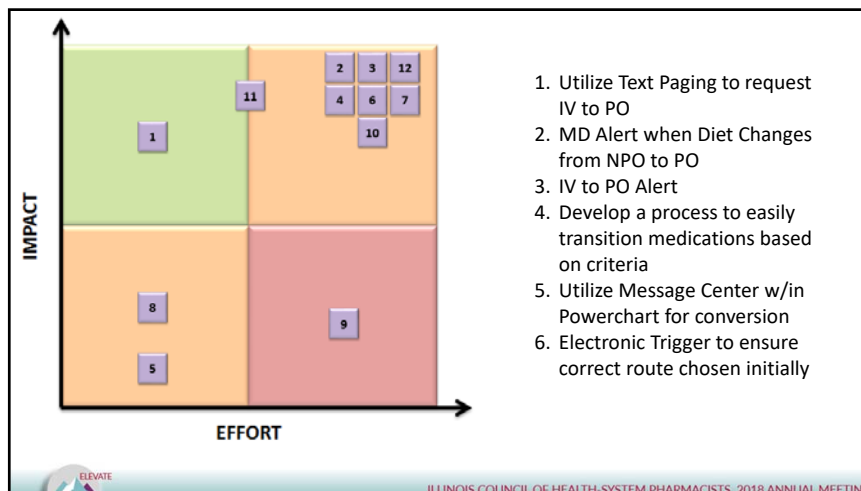
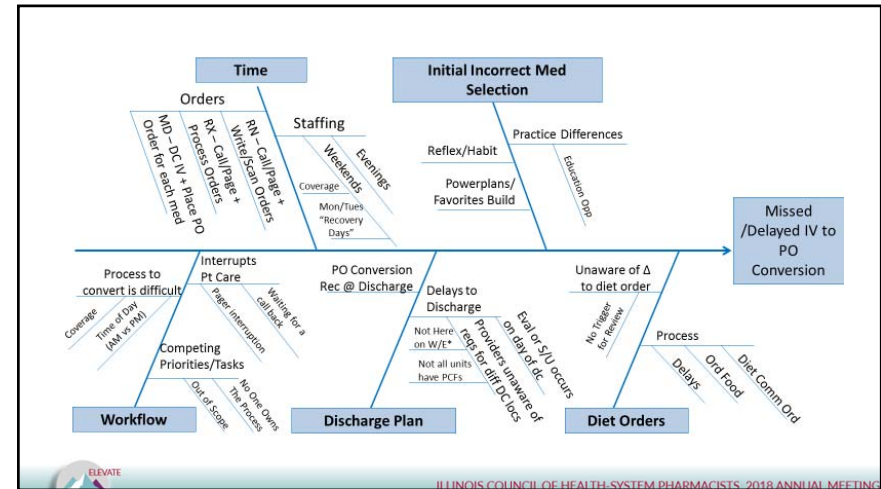
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## Background

- The IV to PO conversion rate was estimated at 73%
- The rate of missed opportunities was estimated at 39%

### Scope of the Project:

- Patients Age > 18 years old
- In-Patients
- Medications:
  - Antimicrobials
  - Anticonvulsants
  - Levothyroxine
  - H<sub>2</sub> Antagonists
  - Proton Pump Inhibitors



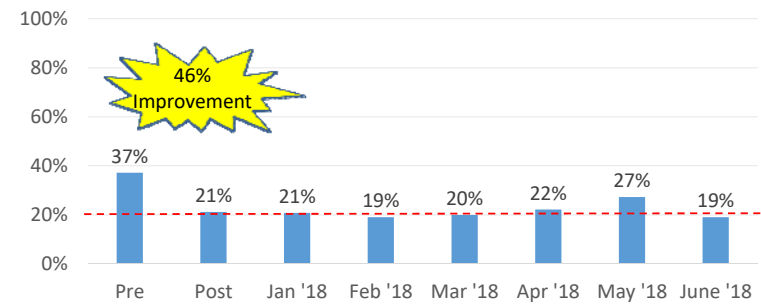


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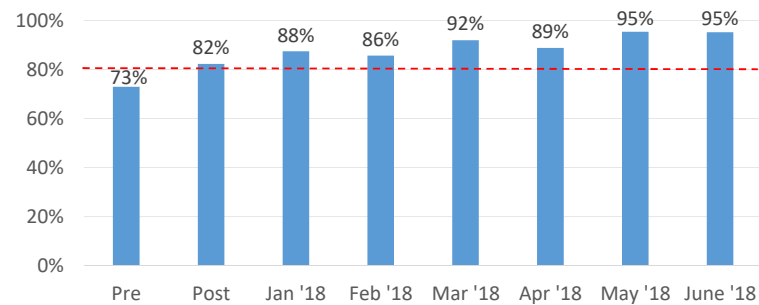
Folder:

Angiotensin Converting Enz CSF
Angiotensin Converting Enzyme
Convert meds to IV
Convert meds to PO
CSF Angiotensin Converting Enz

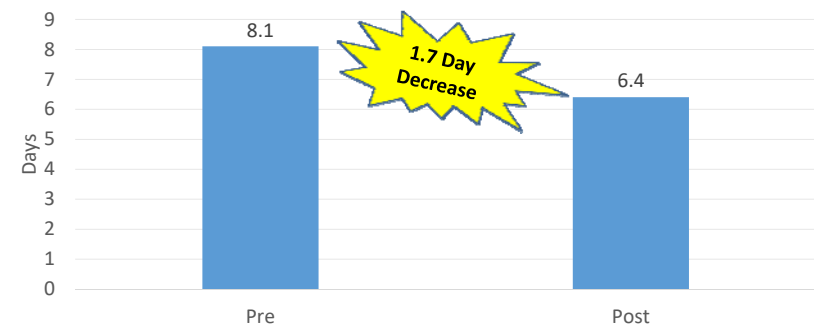
## Rate of Missed Opportunities



## IV to PO Conversion Rate



## Length of Stay





## Project Extensions

- Share Improvements with Pharmacy Departments at Affiliates
- Add more medications to the Automatic IV to PO Policy:
  - Ampicillin-Sulbactam
  - Digoxin
  - Folic Acid
  - Metoclopramide
  - Multivitamin
  - Ondansetron
  - Thiamine
  - Voriconazole



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## Conclusion

- Explore what your EHR offers
  - Engage your IT pharmacist/resources
- Key Elements to a report or worklist
  - Diet Order
  - Specified list of IV medications
  - Group all of the patient's eligible orders
- Multi-disciplinary approach



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Which of the following are improvements can be implemented into the EHR?

- i. Implement an IV to PO Policy for automatic conversion
  - ii. Clinical Pharmacy Worklist
  - iii. EMar Comments
- A. iii only
  - B. i and ii
  - C. i and iii
  - D. ii and iii



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## iMAS: The Solution to Patient Barriers with High Cost Medications

Jordan Johnson, Pharm.D.

Clinical Pharmacist

SwedishAmerican: A Division of UW Health

Disclosure: I do not have any actual or potential conflict of interest in regard to the content discussed in this presentation



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## Learning Objective – Pharmacist and Technician

- Describe the role and patient impact of an inpatient medication access specialist



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## Current Issues

- High cost medications can negatively impact patient's hospital experience
- Lack of education provided on new medications and potential barriers
  - Decreased compliance
  - Increased dissatisfaction
- Potential for readmission due to these factors



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## Current Issues

- Pharmacists do not perform discharge medication reconciliations
  - Performed by nurse or physician
- Lack of awareness of potential costs or dispensing issues with medication
- Lack of education provided to the patient
- Once identified, patient may have already left hospital or refused filling medication



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## Impact on Patient Compliance

- Eaddy, et al., literature review 2012<sup>1</sup>
  - 160 articles assessing cost-sharing, adherence, and outcomes
  - For each \$1 increase in copay, adherence decreased by 0.4% (24 studies)
  - Increased adherence improves clinical outcomes (57 studies)
  - Increased patient cost sharing adversely affects outcomes (19 studies)
- Overall, 85% of studies found negative effect on adherence with increasing cost



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## Impact on Patient Compliance

- CMS National Health Expenditures data
  - Historical and prospective spending patterns
- National health spending is projected to grow at an average 5.6% per year<sup>2</sup>
- Prescription drug spending growth project to grow an average 6.3% per year through 2025



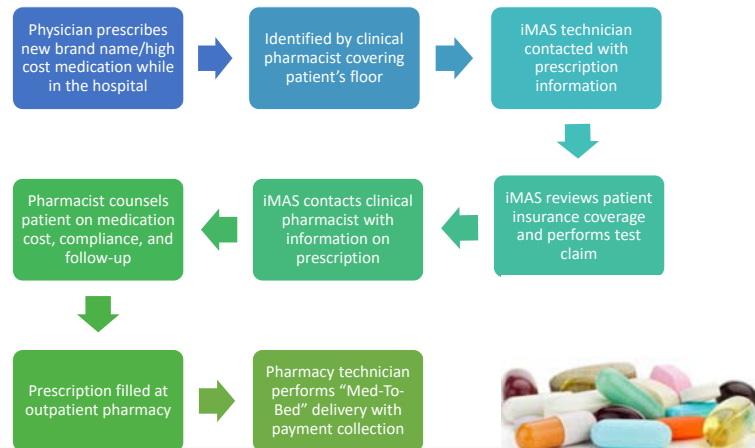
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## iMAS: Inpatient Medication Access Specialist

- Pharmacy technician trained in retail and inpatient setting
- Access to retail pharmacy software as well as inpatient records
- Available Monday through Friday 8:00 am to 5:00 pm
- Performs test claims with patient specific insurance and qualifying coupon cards to find best options for high cost medications prior to discharge



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## Patient Impact

- Average patient savings= \$1875 per month
- Average claims ran per month = 92
  - Prior to April 2018, > 100 claims per month
- Average monthly outpatient pharmacy revenue = \$15,000
  - Recent outbreak of K2 poisonings
- 340B eligible health system



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## Future Goals

- Expansion of iMAS program to cover multiple areas of hospital setting
- oMAS: Out-patient medication access specialist
  - Primary care clinics and ambulatory services
- Improved access to iMAS data collection and documentation
- Improvement in patient capture and follow-up



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## What impact does an iMAS technician have on patient care?

- A. Medication cost savings
- B. Disease state management
- C. Faster turnaround for medications
- D. Improved patient compliance
- E. All of the above
- F. A,C,D



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## What areas are iMAS technicians most applicable?

- A. Inpatient only
- B. Ambulatory care
- C. Cancer centers
- D. All of the above



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## Resources

1. Eaddy M, Cook C, et al. How patient cost-sharing trends affect adherence and outcomes: a literature review. Pharmacy and Therapeutics. 2012;37(1):45-55.
2. Centers for Medicare & Medicaid Services. National Health Expenditure Data. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData>. Accessed August 13,2018



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## Utilizing Lean Six Sigma Methodology to Prevent Medication Omissions at Discharge

Ashlie Kallal, Pharm.D., CLSSBB  
September 15, 2018



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## Conflict of Interest

The speaker has no actual or potential conflict of interest in relation to this presentation.



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## Learning Objective – Pharmacists and Technicians

Identify decision-making tools available to evaluate possible solutions within a quality improvement project.



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## Project Background

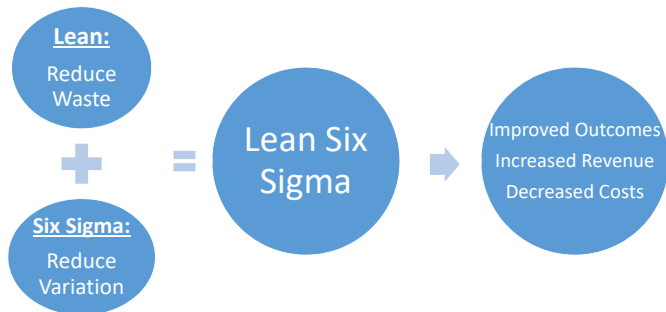
- Lean Six Sigma quality improvement project stemmed from a patient safety event
- Data collection revealed 1 patient/month discharged without warfarin
- Warfarin omissions are associated with:
  - Hospital readmissions
  - Increased medical costs
  - Patient harm, including mortality



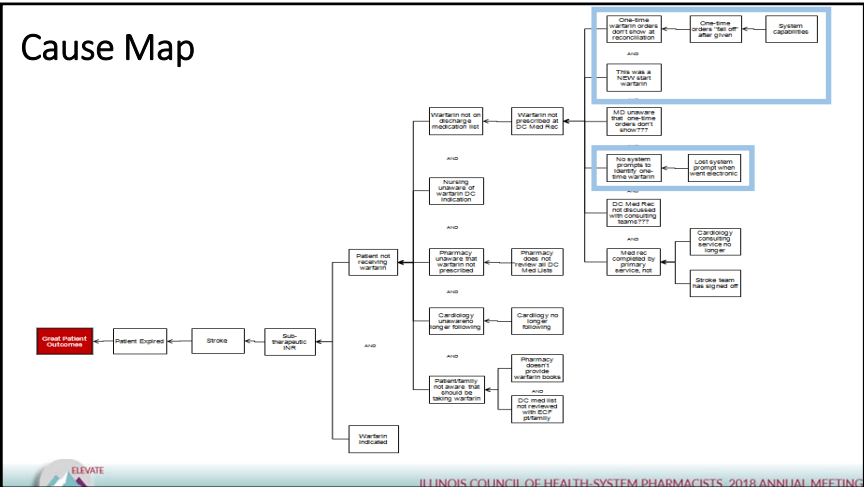
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## What is Lean Six Sigma?

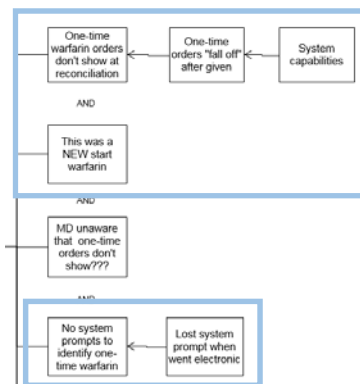
A fact based, data driven problem solving methodology



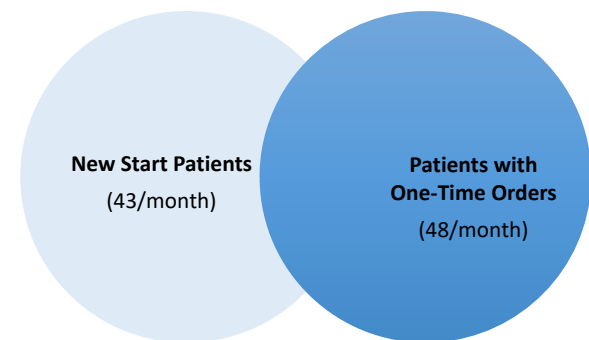
## Cause Map



## Cause Map - Root Causes

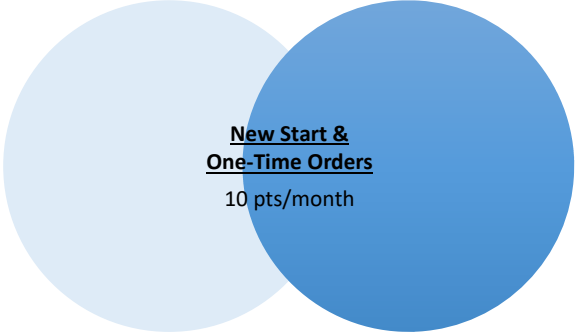


## Warfarin: New Start & One-Time



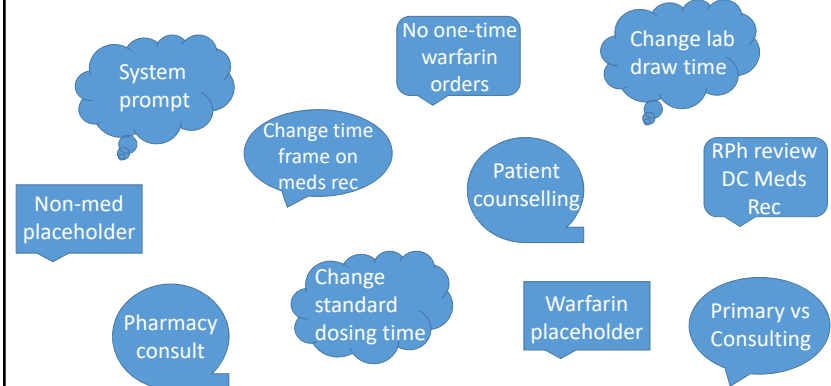
## Warfarin: New Start & One-Time

New Start &  
One-Time Orders  
10 pts/month




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## Warfarin Omission – Possible Solutions



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## Selecting a Solution - Which is best?

- Solution should address the root cause
- What is required to implement?
- What additional data/information is needed?
- Utilize decision-making tools
  - Quality Impact & Effort Matrix
  - Failure Modes and Effects Analysis (FMEA)
  - Stakeholder & Resistance Analysis Tool



Pyzdek T, Keller P. The Six Sigma Handbook. 4th ed. New York, NY: McGraw Hill Education; 2014.

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- Image removed due to copyright

American Society for Quality. Impact Effort Matrix. Available at: <http://asq.org/healthcare-use/why-quality/impact-effort.html>. Accessed 8/18.



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## Warfarin Omission – Impact/Effort Matrix

### Major Effort

- A1 – System Prompt/Reminder
- A2 – Non-med Placeholder
- C1 – Do not allow one-time orders
- D1 – Warfarin (med) Placeholder

### Hard Sell

- B1 – Every warfarin patient to receive counseling
- E3 – RPh to review every DC Meds Rec
- E1 – Pharmacy consult to “oversee” (not manage)
- E2 – Primary team to discuss DC Meds with Consulting Team
- F1 – Change lab draw times
- F2 – Change Warfarin Standard Dosing Time
- G1 – DC Meds Rec to pull in 24 hrs of DC'd Meds

Image removed due to copyright



## Failure Modes and Effects Analysis

Process or Product Name: Process Owner:		Prepared by: FMEA Date (Yr):							Page: of Pages						
Key Process Step or Input	Potential Failure Modes	Potential Failure Effects	S E V	Potential Causes	O C C	Current Controls	D E T	R P N	Actions Recommended	Resp.	Actions Taken	S E V	O C C	D E T	R P N
What is the Process Step or Input?	In what ways can the Process Step or Input fail?	What is the impact on the Key Output Variables once it fails (customer or internal requirements)?	Severity of Effect	What causes the Key Input to go wrong?	How often does it occur?	What are the existing controls and procedures that either prevent or detect failure mode?	Can you detect it?	Risk Priority Number	What are the actions for reducing the occurrence of the cause, or improving detection?	Who is Responsible for the recommended action?	Note the actions taken include dates of completion	Severity of Effect	How often does it occur?	Can you detect it?	Risk Priority Number
1								0							0
2								0							0
3								0							0
4								0							0
5								0							0
6								0							0
7								0							0
8								0							0
9								0							0

Institute for Healthcare Improvement. Failure Modes and Effects Analysis Tool. Available at: <http://app.ihl.org/workspace/tools/fmea/>. Accessed 8/18.

## Warfarin Omission - FMEA



## Failure Modes and Effects Analysis

Process or Product Name		Varian Omission at Discharge -Alert to MD		Prepared by		Achille Katal				
Process Owner				FMEA Date (Yr)		Sep-17				
Key Process Step or Input	Potential Failure Modes	Potential Failure Effects	S E V	Potential Causes	O C C	Current Controls	D E T	R P N	Actions Recommended	Resp.
What is the Process Step or Input?	In what ways can the Process Step or Input fail?	What is the impact on the Key Output Variables once it fails (customer or internal requirements)?	Severity of Effect	What causes the Key Input to go wrong?	How often does it occur?	What are the existing controls and procedures that either prevent or detect failure mode?	Can you detect it?	Risk Priority Number	What are the actions for reducing the occurrence of the cause, or improving detection?	Who is Responsible for the recommended action?
MD completes DC Meds Rec.								0		
1 No warfarin to be reconciled and warfarin omitted from plan.										
2 System alert fires to MD	MD ignores alert	warfarin omission at DC	7		4	no detection	8	224	Require MD response at point of alert firing	MD with MD on individual basis

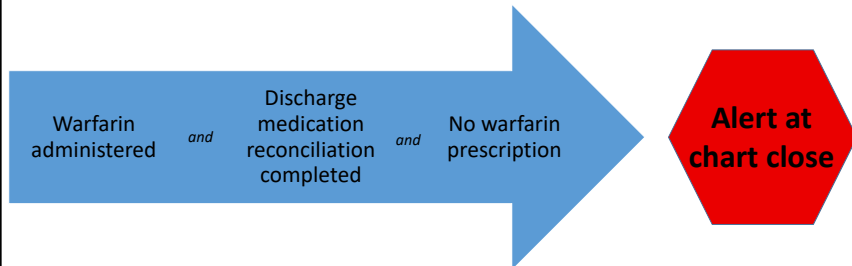
## Stakeholder & Resistance Analysis Tool

Key Stakeholder	Strongly Against	Moderately Against	Neutral	Moderately Supportive	Strongly Supportive

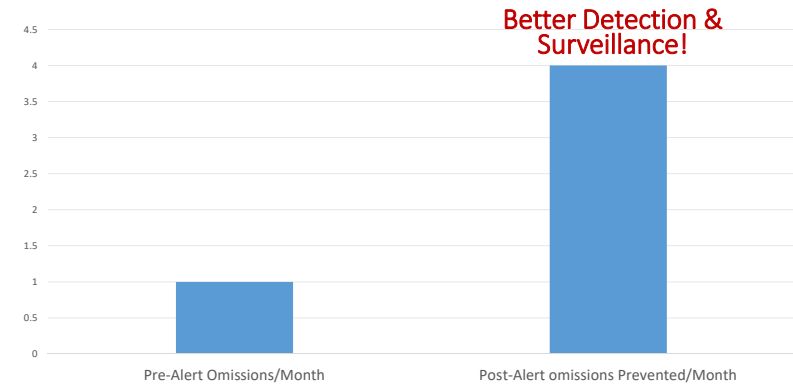
iSixSigma. Preventing Conflicts Through Stakeholder Management. Available at: <https://www.isixsigma.com/implementation/change-management-implementation/preventing-conflicts-through-stakeholder-management/>. Accessed 8/16/18.



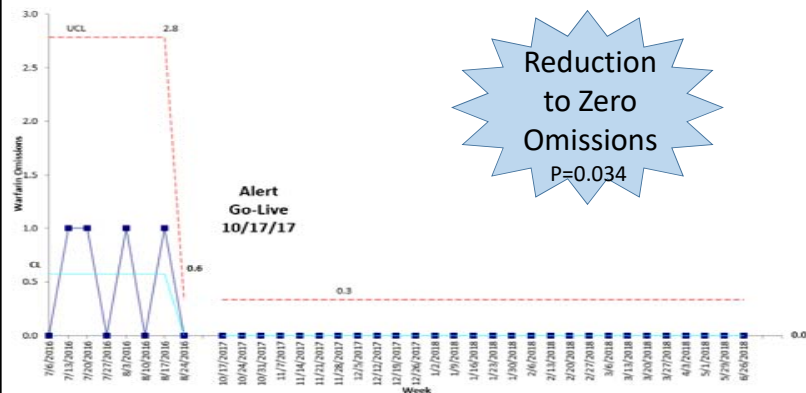
## Improvement: System Alert



## Results – Warfarin Omissions



## Results – Warfarin Omissions



## Applying to YOUR Practice

- Are you at risk for medication omissions at discharge?
- Examine your data
- Be open to new solutions
- Utilize decision-making tools when choosing which solution to implement

Tools that can be utilized to evaluate possible process improvement solutions include:

- A. Failure Modes and Effects Analysis
- B. Stakeholder & Resistance Analysis
- C. Impact & Effort Matrix
- D. All of the above



# Quality Improvement Pearls - Reducing Hazardous Drug Exposure

## Self-Assessment Questions

1. Hazardous Drug Exposure has been known to cause all of the following except?
  - A. Teratogenicity
  - B. Reproductive toxicity
  - C. Organ toxicity
  - D. Cardiotoxicity
  
2. USP 800 requires the use of a Closed System Transfer Device (CSTD) for \_\_\_\_\_?
  - A. chemotherapy administration only
  - B. chemotherapy compounding only
  - C. both chemotherapy administration and compounding
  - D. neither – CSTD use is optional

# Deconstructing Constructive Feedback

Saturday, September 15, 2018  
9:30 – 11:30 AM

The speakers have no conflicts of interest to disclose



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## Presenters

Jill Borchert, PharmD, BCPS, BCACP, FCCP

Midwestern University Chicago College of Pharmacy

Jennifer Arnoldi, PharmD, BCPS

Southern Illinois University Edwardsville School of Pharmacy

Justin Schmidt, PharmD, BCPS, BC-ADM

Midwestern University Chicago College of Pharmacy

Tiffany Scott-Horton, PharmD, BCACP

University of Illinois at Chicago College of Pharmacy

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## Unconstructive Feedback

- Mean Tweets



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## Unconstructive Feedback: Mean Tweets

*'Share your Mean Tweet'*



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## Making it a Positive Experience

- Feedback does not need to be uncomfortable
  - For the one giving feedback
  - For the one receiving feedback
- Poor feedback<sup>1</sup>
  - Poor performance goes uncorrected
- Increases confidence, helps to identify strengths/weaknesses in building skills<sup>2</sup>
  - Who
  - When
  - Where
  - How
  - What



1. Cantillon P. BMJ 2008;337:a1961. 2. Chur-Hansen A. Acad Psychiatry. 2005;29:66-8.

## Practice Setting

- A. Health-system, acute care
- B. Community pharmacy
- C. Ambulatory care pharmacy
- D. Specialty pharmacy
- E. Other

## Direct or Indirect Reports/Manager

- A. Technicians
- B. Pharmacists
- C. Both technicians and pharmacists
- D. Other

## Type of Precepting

- A. Technician Trainees
- B. IPPE Students
- C. APPE students
- D. PGY1 Residents
- E. PGY2 Residents



## Precepting/Managing Experience

1. 2 years or less
2. 3-5 years
3. 6-10 years
4. 11 years or more



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## Learning Objectives

At the end of this presentation, **pharmacist/technician** participants should be able to:

1. Differentiate between feedback and evaluation
2. Identify factors that enhance or diminish the impact of feedback
3. Apply methods of effective feedback for learners, employees and/or peers
4. Propose ways to seek and incorporate feedback for self-development



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## Feedback Giver & Feedback Receiver

“Teacher”



“Learner”



- Preceptor/Student
- Preceptor/Resident
- Pharmacist/Technician
- Technician/Technician
- Peer/Peer
- You/trainee



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## We're here to get better at this!

### • Better feedback:

- Residency accreditation:<sup>1</sup>
  - **Effective** criteria-based feedback as an area of partial-compliance or non-compliance
- Disconnect:<sup>2</sup>
  - 90% of preceptors feel comfortable providing feedback
  - Less than 60% of the residents indicated that their preceptors provided **effective** verbal and written feedback

### Given more often:

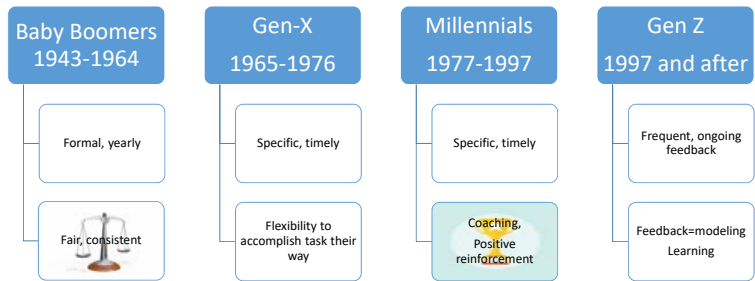
*“More feedback would have been helpful. I would consider having time every week for feedback instead of only mid-module.”*

1. ASHP Communique. 2. Hartzler ML, et al. Am J Health-Syst Pharm 2015; 72: 1305-14.



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## Generations & Feedback



Am J of Health-Syst Pharm 2005;62: 519-524. HBR "Managing People from 5 Different Generations". Forbes "Generational Differences: When They Matter and When They Don't". Forbes "10 Tips for Communication Across Generations."

## Feedback vs. Evaluation

### Feedback

- Formative
- Frequent, ongoing
- Specific, criteria-based

### Evaluation

- Summative
- At end, intermittent
- Overall development of a skill relative to a standard

Weitzel KW. Am J Health-Syst Pharm. 2012; 69:1588-99.

## Deconstructing Feedback: Case Study

Who?

APPE Student with strong clinical skills and confidence  
PGY1 Resident lacks confidence and is struggling  
Preceptor is experienced, but busy

Where?

Faculty office

When?

Week 5 of a 6-week rotation

## Deconstructing Feedback: Case Study

Image Courtesy of Craig Cox, PharmD and Texas Tech



## Deconstructing Feedback: Case Study

- What is wrong in this scenario?



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## Setting the Stage: Where, Why & Who

Jennifer Arnoldi, PharmD, BCPS

Southern Illinois University Edwardsville School of Pharmacy



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*"If we're growing, we're always  
going to be out of our comfort  
zone."*

—John Maxwell



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## Why: The Importance of Good Feedback

- Reinforce good practice and behavior
- Correct performance with guidance *how* to improve
- Encourages dialogue and rapport
- Builds skills learner needs for continuous professional development



1. Cantillon P. BMJ 2008;337:a1961. 2. Wisneski SS. The Effective Pharmacy Preceptor 2017.  
3. Components of the CPD Cycle. ACPE 2011. Permission available at: <https://www.acpe-accredit.org/pdf/CPDCycleTermsOfUseNov2014.pdf>

## Why Feedback Sometimes Fails

- Uncomfortable pointing out negative behavior
- Lack of time
- Not specific enough
- Experiences with previous learners



Wisneski SS. The Effective Pharmacy Preceptor 2017

## Setting the Expectations

Define Goals and Objectives	Communicate	Set Aside Time	Make it Clear
<ul style="list-style-type: none"> <li>• Rubrics or job descriptions</li> <li>• Orient the learner</li> </ul>	<ul style="list-style-type: none"> <li>• How and when it will occur</li> <li>• What you expect from them</li> </ul>	<ul style="list-style-type: none"> <li>• Regularly scheduled vs impromptu</li> <li>• Aim for manageable blocks of time</li> </ul>	<ul style="list-style-type: none"> <li>• "I am giving you this feedback"</li> <li>• "I have some feedback for you"</li> </ul>

Wilkinson S. Hosp Pharm 2013;48(1):26-32.

## Who

- You + the learner
- Make it clear if you have obtained feedback from other sources
- Try to individualize as much as possible
  - Evaluate any growth the learner has shown
  - Consider learner's personality and strengths
  - Maintain learner's dignity, self-esteem, and confidence

Wilkinson S. Hosp Pharm 2013;48(1):26-32.

## Where

- Neutral, private place
- Setting aside one-on-one time
  - Shows appreciation
  - Underlines the importance of the interaction
  - Reinforces the teacher-learner relationship
- Limits distractions and interruptions



Wilkinson S. Hosp Pharm 2013;48(1):26-32.

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## When: Activities Prompting Feedback

### Tasks

- Projects or presentations
- New responsibilities

### Skills

- Patient or colleague interactions
- New or improved job skills

### Professional Behavior

- Punctuality and attendance, dress code
- Attitude, respect, responsibility

## When: The Feedback Session



- As close to the event as possible
  - Helps with recall
  - Provides learner opportunity to continue practicing
- Try to limit the amount of information per session
  - Discussing too much can be overwhelming
  - Focus on no more than 2-3 issues per session
  - Prioritize your feedback and make note of what to discuss at a later time

1. Cantillon P. BMI 2008;337:a1961. 2. Wilkinson S. Hosp Pharm. 2013;48(1):26-32.

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## When to Involve Others

- Trust your instincts
- Early contact is best
  - Technician learner → Supervisor or manager
  - Student learner → Office of Experiential Education (OEE)
  - Resident learner → Residency Program Director (RPD)
- Human resources?
- Expected outcome: advice vs intervention
- Documentation

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## Tips from OEE

- We can't help if we don't know!
- We're here to support you, the student, and the learning experience
- We'll be your sounding board, second opinion, or strategic partner
- Information that the school is able to share about a student may vary
  - "Has this been a concern before?"
  - Learner performance may be different in various settings



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## Common Concerns

- From preceptors / supervisors
  - "But they're a good person" or "They're trying hard"
  - The feedback isn't sinking in
- From learners
  - Not recognizing when feedback has been given
  - Failure to understand where the feedback has come from
- From my perspective
  - Feedback that is too general
  - Lack of documentation



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## Methods for Feedback: Traditional Methods

Tiffany Scott-Horton, PharmD, BCACP  
University of Illinois at Chicago College of Pharmacy



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## Informal vs. Formal Feedback

### Informal

- Unplanned
- Frequent
- **Specific\***
- In small doses
- Given in context of the job function(s)

### Formal

- Planned
- Infrequent
- **Specific\***
- Review longer spans of time
- Discuss observations or trends of the job function(s)



Medical Teacher, Vol. 24, No. 3, 2002 pp. 245-248, Pitkanen, H., Lukka, K. Formal and informal feedback in management accounting. Taking a look beyond the balanced scorecard. Volume 6, Issue 14.



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## Informal vs. Formal Feedback

Do you actively seek feedback?

- a. Yes
- b. No



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## Informal vs. Formal Feedback

What type of feedback do you usually prefer?

- a. Informal
- b. Formal



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## Informal vs. Formal Feedback

Which type of feedback session can contain the most surprises?

- a. Informal
- b. Formal



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## Keys to Success for Informal Feedback

- Avoid negative non-verbal cues that suggest disapproval
- Limit feedback to useable information for the trainee
- Allow the learner to evaluate the situation
- Given at the time of the event or action
- Be aware of an audience



Medical Teacher, Vol. 24, No. 3, 2002 pp. 245-248  
Perspect Med Edu, No 4, 2015 pp. 284-299



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## Keys to Success for Formal Feedback

- Ensure trainee is aware that a feedback session will occur
- First hand data and direct observation are preferred
- The trainee should agree with the assessment
- Encourage trainee to self-assess
- Involve the trainee in resolutions



Medical Teacher, Vol. 24, No. 3, 2002 pp. 245-248  
Perspect Med Edu. No 4, 2015 pp. 284-299

## Group Discussion: Informal vs. Formal Feedback

### Scenario

**Suzi (Technician #1)** : Hi Stan (**Manager**), do you mind if I meet with you briefly to discuss some things I've noticed in the pharmacy?

**Stan**: Sure Suzi, tell me what's going on?

**Suzi**: I've noticed that Jim (**Technician #2**) takes too long to put away the order and I'm often left filling all the STAT orders and answering the phones. I get really backed up and the pharmacists become angry because they think I'm moving too slow.

**Stan**: Thanks for letting me know Suzi, I'll take care of it.

## Group Discussion: Informal vs. Formal Feedback

#1. Does this situation require feedback for Jim (Technician #2)? If so, what type of feedback is warranted formal or informal?

#2. Is Suzi's account considered first-hand or second hand?

#3. How could the manager involve Technician #1(Suzi) in the solution?

## The Sandwich Method



Constructive Compliment

Constructive Criticism

Constructive Compliment

Journal of Behavioral Studies in Business Volume 7 – September, 2014

## The Sandwich Method – Role Play

**3 roles: Manager(Stan), Technician #2 (Jim), Observer/Coach**

### **Situation:**

Stan decides to observe **Technician #2** (Jim) during his daily tasks. The manager notes that Jim is thorough and he puts away the order correctly and neatly. Stan also notices that while Jim puts the order away he pulls out his phone to text every time he goes to the back of the store and he is talking more with the other employees. Overall, it took Jim 90 minutes to put away the order when it should take approximately 45-60 minutes.

Stan also notices that **Technician #1** (Suzi) is working quietly and diligently on the floor to meet the demands of the workflow.

### **Role Play:**

How should the manager utilize “The Sandwich Method” to provide feedback to Technician #2?

## The Sandwich Method

### **Pros**

- Easier
- Less anxiety
- Improves communication
- Increase receptivity of the person being coached

### **Cons**

- Distracts from the message
- Diminishes corrective value
- Dilutes the severity of consequences
- Overtime, may cause anxiety in the person receiving feedback

Journal of Behavioral Studies in Business Volume 7 – September, 2014

## Sandwich Method – *Alternative*

### **Correct Correcting – 9 Step Process**

1. Plan for the discussion
2. Keep positives and negatives separate
3. Time discipline so it's not too soon or too late
4. Focus on the issue
5. Relate the issue to how it impacts business
6. State consequences if behavior does not improve
7. Identify the proper behavioral change that's expected
8. Ask how the manager can help the worker
9. Express confidence in the employees ability to improve

Journal of Behavioral Studies in Business Volume 7 – September, 2014

## Correct Correcting Role Play

**3 roles: Manager (Stan), Technician #2 (Jim), Observer/Coach**

### **Situation:**

Stan decides to observe **Technician #2** (Jim) during his daily tasks. The manager notes that Jim is thorough and he puts away the order correctly and neatly. Stan also notices that while Jim puts the order away he pulls out his phone to text every time he goes to the back of the store and he is talking more with the other employees. Overall, it took Jim 90 minutes to put away the order when it should take approximately 45-60 minutes.

### **Role Play:**

How should the manager utilize the 9 step process of “Correct Correcting” to provide feedback to Technician #2?

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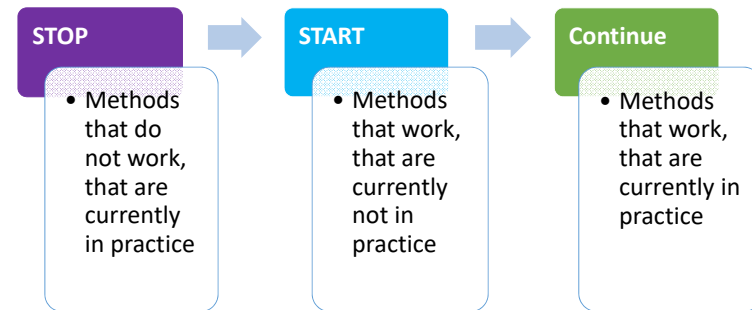
## Correct Correcting Plan

1. Inform Jim that you would like to meet on a specific day/time
2. Discuss the problematic behavior
3. Ensure that the meeting is within 24-48 hours of noted behavior (may be sooner is scheduling permits)
4. During the meeting focus only on the problematic behavior
5. Relate the impact his behavior has on the other technicians/workflow
6. Determine what the consequence will be and alert the learner that it will be enforced if improvements are not noted by a specified day/time (giving a time frame is essential, because everyone's timeline for improvement may be different and you need the learner to understand your expectations).
7. Your expectation is that the order is put up correctly, in a timely manner, with minimal distraction so that the technician can resume regular workflow as quickly as possible.
8. Ask what you can do to help
9. Express confidence in Jim to get it right



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## Stop, Start, Continue Model



Hoon A, et al. Use of the 'Stop, Start, Continue' method is associated with the production of constructive qualitative feedback by students in higher education, *Assessment & Evaluation in Higher Education*, 2015 40:5, 755-767



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## Benefits of the Stop, Start, Continue Model

- Easy to remember
- Individual or team feedback
- Effective in formal or informal settings
- Useful when gathering feedback from multiple people



Hoon A, et al. Use of the 'Stop, Start, Continue' method is associated with the production of constructive qualitative feedback by students in higher education, *Assessment & Evaluation in Higher Education*, 2015 40:5, 755-767

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## Stop, Start, Continue Model – Role Play

**3 roles: Manager, Technician #2 (Jim), Observer/Coach**

### Situation:

Stan decides to observe **Technician #2 (Jim)** during his daily tasks. The manager notes that Jim is thorough and he puts away the order correctly and neatly. Stan also notices that while Jim puts the order away he pulls out his phone to text every time he goes to the back of the store and he is talking more with the other employees. Overall, it took Jim 90 minutes to put away the order when it should take approximately 45-60 minutes.

**Technician #1 (Suzi)** is working quietly and diligently on the floor to meet the demands of the workflow.

### Role Play:

How should the manager utilize the Stop, Start, Continue Model to provide feedback to Technician #2?



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## Group Discussion

### Scenario

Crystal Pharmacy has been backed up all day and short staffed. It's at the end of the day and the pharmacist realized that the perpetual inventory is not working and it has to be entered manually. The pharmacist has several prescriptions to verify and prior authorizations to work on before close. The pharmacist asks the technician to enter the order manually in preparation for the next day. The technician replies, "That's not my job".

### **Discussion:**

Which feedback technique would you apply here and why?



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## Methods for Feedback: Traditional Methods + Innovation

Justin Schmidt, PharmD, BCPS

Midwestern University Chicago College of Pharmacy



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How would you describe the picture?



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How would you describe the picture?



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## Connecting to PGY-1 Standards

- Address progression & methods of improvement (if applicable)
  - Frequent
  - Immediate
  - Specific
  - Constructive
- Adjust learning activities

ASHP:2016 [www.ashp.org](http://www.ashp.org)

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## Connecting to PGY-1 Standards

- Verbal required for formative feedback (during rotation)
- Verbal + written for summative *evaluation*
- Written: okay for SOAP notes, evaluations of presentations/projects
- Specific recommendations if unsatisfactory progression

ASHP:2016 [www.ashp.org](http://www.ashp.org)

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## PharmAcademic Formative Feedback

- Three options:
  - Documentation of verbal feedback
  - Written feedback
  - Generate a formative assessment
    - Create a custom assessment
- Can upload files
- Map feedback to goals and objectives

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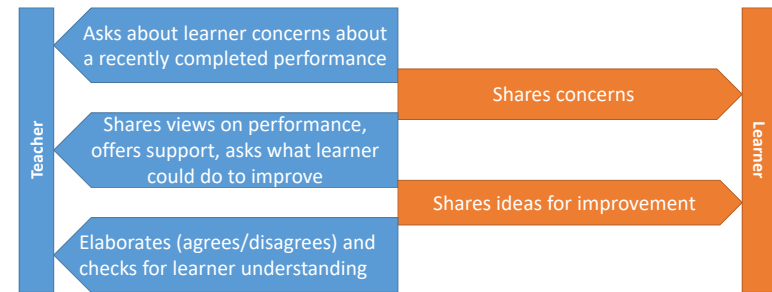
Method:  
Reflective  
Feedback  
Conversation

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## Reflective Feedback Conversation Method

- As we progress through the next few slides and roleplay, please add comments you have regarding the Reflective Feedback Conversation method

## Reflective Feedback Conversation Method



Cantrill P. BMJ 2008;337:a1961.

## Speaker Role Play: PGY-1 Midpoint

- Midpoint formative feedback
- PGY-1 resident on their first rotation
- Last experience with hospital pharmacy was nearly a year ago
- We will try using the reflective feedback conversation

## Speaker Role Play: PGY-1 Midpoint

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>Teacher perspective</li> <li>Key observations               <ul style="list-style-type: none"> <li>Overlooked positive blood cultures</li> <li>Did not identify over-replacement of Na (increase was &gt;10 mEq/L in one day)</li> <li>Empiric coverage was initiated with meropenem for UTI but most recent ESBL was &gt; 5 years prior to admission (coverage not really needed)</li> </ul> </li> <li>Synopsis               <ul style="list-style-type: none"> <li>During the first half of the rotation, the resident struggled to evaluate and identify interventions for her patients. Most of her efforts went into reviewing progress notes (which she did a good job with) and collecting patient information.</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Learner perspective</li> <li>Self-evaluation               <ul style="list-style-type: none"> <li>Keeping up with big patient load</li> <li>Following up with most questions posed to me (how much of a change in Na in one day is safe)</li> <li>Becoming more comfortable with medical record and expectations</li> </ul> </li> <li>Synopsis               <ul style="list-style-type: none"> <li>I am appropriately progressing in the rotation and learning a lot.</li> </ul> </li> </ul> |
|---|--|

## Role Play - Dialog

While experience can help, I recommend quickly reviewing literature/guideline recs for patients' primary problems. This will improve your effectiveness as a pharmacist on the team. Does that make sense to you?



It will come with experience



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## Reflective Feedback Conversation Method

- How you think this method worked in this situation?

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## Audience Role Play: PGY-1 Patient Work-up

- Week 4 formative feedback
- Same resident (first rotation, limited experience)
- Near the end of week four, you watch the resident work-up a patient and have them talk through the process
- Try using the reflective feedback conversation in the following scenario

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## Audience Role Play: PGY-1 Patient Work-up

### Teacher observations

- Appears frustrated with the patient monitoring form provided to them
- Reads nearly every progress note start to finish
- Adds a medication to their inpatient med list after reading this in a progress note
- Recommends increasing insulin without reviewing administration record

### Learner comments

- I'm working on getting used to the tool to collect patient information
- I get in at 6AM but I barely have time to print my monitoring forms before pre-rounds
- I know a lot of details about patients, but I feel like I'm still missing how everything fits together

*If learner targeted notes/sections to read, more time to:  
Review administration and orders sections of EMR  
Review guidelines/optimal treatment vs current therapy  
Think about how "pieces fit together"  
Learner could create a form/tool that is meaningful for them*

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## Reflective Feedback Conversation Method

- How you think this method worked in this situation?

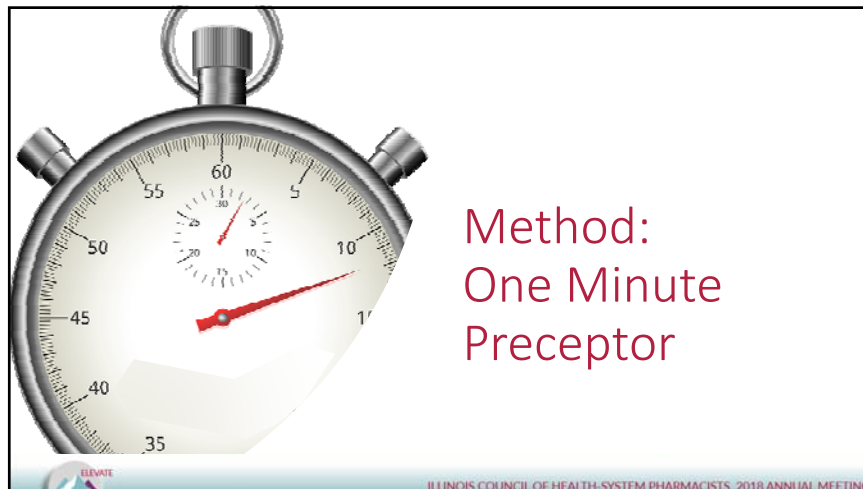
## Reflective Feedback Conversation Method

### Pros

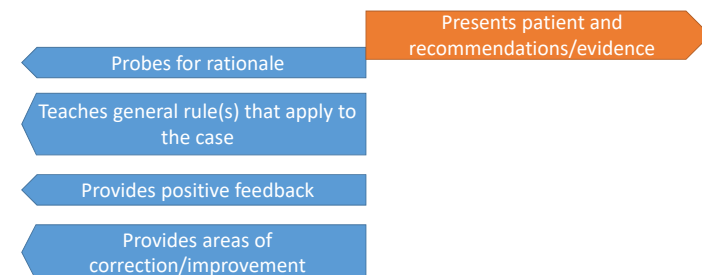
- Learner-centric:
  - Focuses on what matters to learner
  - Helps learner develop life-long ability to self-assess and identify strategies for improvement

### Cons

- Does not work well for summarizing several observations
  - *Awkward to keep asking about learner's concerns*
- Could miss some important feedback noted by teacher



## One-minute Preceptor Model (AKA Five-Step Microskills Model)



Neher JO. J Am Board Fam Pract. 1992;5:419-24.

## One-minute Preceptor Model (AKA Five-Step Microskills Model)

### Pros

- Focus on learner's reasoning process
- Supported by literature
- Well-suited for patient discussions
  - For any repetitive presentation of problem-solving

### Cons

- Does not solicit input from learner (esp regarding self-evaluation and how to improve)
- Might not be acknowledged as feedback

Weitzel KW. Am J Health-Syst Pharm. 2012; 69:1588-99.

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## Creating a "Feedback feed" to document One Minute Preceptor Feedback



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### "Feedback feed" screenshots

When clicked:  
Learner menu displays

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### "Feedback feed" screenshots

Default:  
Send email each time file closes

Alternative:  
Send email with button click

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## “Feedback feed” screenshots

Send Cc... Subject Feedback

Your feedback notes include the following:

Date	Request	Comment	Standard
7/15/2018	Please independently evaluate CHADS2/Vasc.	Would consider PAD and indications (statin).	R1.1.4 - Analyze and assess information on which to base safe and effective medication therapy.
7/15/2018	Please review non-prostacyclin analogs for FC III PAH w/ neg reversibility testing.	Please review non-prostacyclin analogs for FC III PAH w/ neg reversibility testing.	R1.1.3 - Collect information on which to base safe and effective medication therapy.
7/18/2018	Please review possible drug causes of thrombocytopenia.	Please make sure to allow enough time to evaluate all the patients (didn't get around to a patient w/ an opportunity for antibiotics de-esc).	R1.1.3 - Collect information on which to base safe and effective medication therapy.
7/18/2018	Please review adherence w/ naloxone for patient with ETOH w/d	Please review previous course of ertapenem and consider options if the same organism grows.	R1.1.3 - Collect information on which to base safe and effective medication therapy.
7/18/2018	Watch for expiration of medications (e.g. levetiracetam).	Please review possible drug causes of thrombocytopenia.	R1.1.3 - Collect information on which to base safe and effective medication therapy.
7/18/2018	Would review electrolyte repletion/administration in previous 24 hrs when this is a central issue...will work to configure CPBS.	Please review adherence w/ naloxone for patient with ETOH w/d	R1.1.4 - Analyze and assess information on which to base safe and effective medication therapy.
7/18/2018	Watch for expiration of medications (e.g. levetiracetam).	Watch for expiration of medications (e.g. levetiracetam).	R1.1.4 - Analyze and assess information on which to base safe and effective medication therapy.
7/18/2018	Would review electrolyte repletion/administration in previous 24 hrs when this is a central issue...will work to configure CPBS.	Would review electrolyte repletion/administration in previous 24 hrs when this is a central issue...will work to configure CPBS.	R1.1.4 - Analyze and assess information on which to base safe and effective medication therapy.
7/18/2018	Watch for expiration of medications (e.g. levetiracetam).	Please review drug causes of lactic acidosis.	R1.1.4 - Analyze and assess information on which to base safe and effective medication therapy.
7/18/2018	Watch for expiration of medications (e.g. levetiracetam).	Please review administration of apixaban in PEG tube	R1.1.3 - Collect information on which to base safe and effective medication therapy.

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## Balancing time and quality

- Unrefined comments
  - Overlooked + BICx
- Comments + suggestions
  - Overlooked positive blood cultures
  - Please create a method of ensuring systematic evaluation
- Comments + suggestions + associated goal/obj
  - Overlooked positive blood cultures
  - Please create a method of ensuring systematic evaluation
  - R1.1.3 - Collect information on which to base safe and effective medication therapy

## Mapping feedback to goals/objectives

- Vast majority of observations in one of the following
  - Collect information...
    - Patient ...have the needed data/info at their disposal
    - Literature/drug info...identify appropriate resources to apply to patient
  - Analyze and assess information...
    - Patient...identify problems in drug therapy
    - Literature/drug info...interpret information from resource
  - Design therapeutic regimens & monitoring plans
    - Patient...identify solutions
    - Literature/drug info...apply to patient

## “Feedback feed” assessment

### Pros

- Efficient (integrated into patient care)
- Timely feedback – limits overwhelming detail at midpoint/final
- Log of questions/date helpful to refer to on occasion

### Cons

- Does not encourage self-evaluation
- Potentially demotivating if mostly negative comments

### Informal feedback from students/residents:

- Helpful to know how things are going each day
- Useful to remember what to look up

## Creating a “Feedback feed”

- Macros in Excel patient monitoring form
  - For an overview of macros in Microsoft products, [click here](#)
- File and user guide available for 90 days at:
  - [Link \(https://tinyurl.com/y8zk6czp\)](https://tinyurl.com/y8zk6czp)



## Feedback for You: Summary, Planning and Toolkit

Jill Borchert, PharmD, BCPS, BCACP, FCCP  
Midwestern University Chicago College of Pharmacy

## Summary

- Feedback is IMPORTANT
- Good feedback is SPECIFIC, ONGOING
- Feedback options
  - Setting
  - Type: Formal vs. Informal
  - Traditional Techniques
    - Start/Stop/Continue, Sandwich, Correct Correcting, One minute preceptor, Reflective feedback
  - Innovation/technology
    - Feedback feed
- Get to know your learner
- Have a few techniques ready for TIMELY feedback



## Planning

- What's your take home technique?
- Set a reminder
  - Reflect on pros/cons



## Feedback Toolkit

### Clinical Medical Education

- Cantillon P, Sargean J. [Teaching Rounds: Giving feedback in clinical settings](#). BMJ. 2008; 337:a1961.
- Lefroy J et al. [Guidelines: the do's and don'ts and the don't knows of feedback for clinical education](#). Perspect Med Educ 2015; 4:284-299.
- Bing-You R, Hayes V, et al. [Feedback for learners in medical education: What is known? A scoping review](#). Acad Med 2017;92:1346-1354.

### Pharmacy Precepting

- Weitzel, KW, Walters EA, Taylor J. [Teaching clinical problem solving: A preceptor's guide](#). Am J Health-Syst Pharm. 2012;69:1588-99.

### Management & Generations

- Knight R. [Managing People from 5 Generations](#). Harvard Business Review. September 25, 2014.



## Questions





## The Opioid Crisis: Effective Strategies to Turn the Tide

Adam Bursua, Pharm.D., BCPS  
 Laura Meyer-Junco, Pharm.D., BCPS, CPE  
 Mary Lynn Moody, BSPHarm  
 Annette Hays, Pharm.D., BCPS  
 Kevin O. Rynn, Pharm.D., FCCP, DBAT  
 Christopher Shriever, MS, Pharm.D.

The speakers have no conflicts of interest to disclose



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## Responsible Opioid Prescribing

Laura Meyer-Junco, PharmD, BCPS, CPE  
 Clinical Assistant Professor, UIC College of Pharmacy at Rockford  
 Clinical Pharmacist, MercyHealth and Hospice Care of America

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## Learning Objectives – Pharmacists and Technicians

1. ***Develop an approach to responsible opioid prescribing, reducing the risk of misuse, abuse, and diversion of opioids.***
2. Evaluate the role prescription drug monitoring programs play in decreasing opioid misuse and abuse.
3. Order the effectiveness of various types of interventions to ensure the safe use of opioid therapy.
4. Formulate effective strategies to influence positive changes in the opioid medication use process in a health care organization.



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**Definitions**

**01**  
**Aberrant Drug Behavior**  
Any drug-related deviation from the medical plan

**02**  
**Abuse**  
Use of an opioid for a non-therapeutic intent


**03**  
**Misuse**  
Inappropriate use of a drug, whether deliberate or unintentional (therapeutic intent)

**04**  
**Pseudoaddiction**  
Drug-seeking behavior from undertreatment of pain

**05**  
**Chemical Coping**  
Reliance on a drug for psychological stability

**06**  
**Diversion**  
Transfer of a prescription from a lawful to unlawful method of distribution

**07**  
**Addiction ("Substance Use Disorder")**  
Out-of-control, compulsive drug use despite harm to health, relationships, finances



Webster L, et al. Avoiding opioid abuse while managing pain. North Branch, MN: Sunrise River Press; 2007.  
Am J Psychiatry 2016; 173(1): 18-26  
Mayo Clin Proc 2009; 84 (7): 593-601

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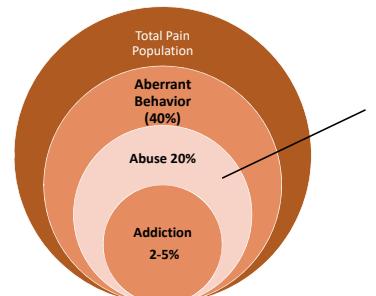
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**"All addicted people are abusers, but not all abusers are addicted"**



What is driving the abuse or misuse?

- Chemical coping
- Uncontrolled pain
- Misunderstanding of treatment plan

Pain Med 2005; 6(6): 432-442.

Webster L, et al. Avoiding opioid abuse while managing pain. North Branch, MN: Sunrise River Press; 2007.

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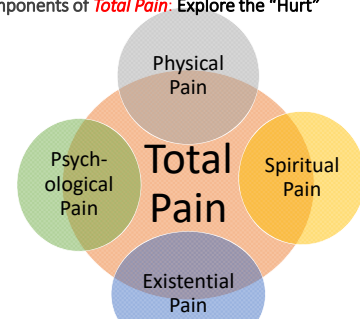
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**Recognize Components of *Total Pain*: Explore the "Hurt"**



Journal of Hospice and Palliative Nursing 2008; 10(1): 26-32.

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### Guidelines for Opioid Prescribing in Chronic Pain\*

CDC Guideline for Prescribing Opioids for Chronic Pain (2016)

VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain (2017)

Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (American Pain Society and American Academy of Pain Medicine, 2009)

These guidelines do not apply to cancer pain or end-of-life care

Chronic Pain = pain lasting longer than 3 months

MMWR 2016; 65(1):1-49  
<https://www.healthquality.va.gov/guidelines/Pain/cot/>

J Pain 2009; 10 (2): 113-130

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### Guideline Consensus: Non-Opioids *First*

**CDC #1**

**"Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain.** Clinicians should *consider opioid therapy only* if expected benefits for both pain and function are anticipated to outweigh risks to the patient.

- Evidence for **short-term** use of opioids (trials < 12 weeks)
- Insufficient evidence** to determine if pain relief is sustained and function improves with **long term opioid therapy.**
- Risks** of long term therapy are **known**

MMWR 2016; 65(1):1-49  
<https://www.healthquality.va.gov/guidelines/Pain/cot/>

**VA #1**

- "We recommend against initiation of long-term opioid therapy for chronic pain
- We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments
- When pharmacologic therapies are used, we recommend non-opioids over opioids."**

- Literature review conducted found **no studies** evaluating opioid therapy > 16 weeks

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**APS**

"Clinicians **may** consider a trial of chronic opioid therapy (COT) as an option if chronic non-cancer pain (CNCP) is **moderate or severe**, pain is having an adverse impact on **function or quality of life**, and potential therapeutic benefits outweigh or are likely to **outweigh potential harms** (strong recommendation, low-quality evidence)"

J Pain 2009; 10 (2): 113-130

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Guidelines Consensus: Risk Assessment *before* Opioid Initiation

CDC #3 #8-10

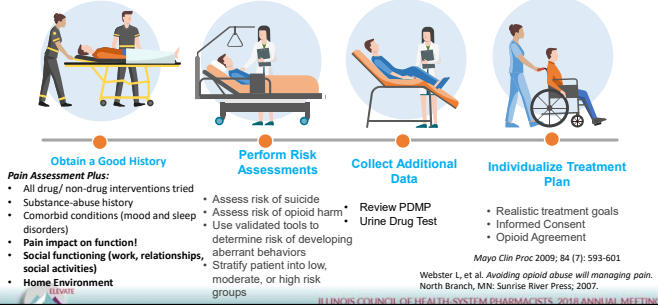
VA #7-8

APS #1-2

Discuss known risks and realistic benefits of opioid therapy AND patient/clinician responsibilities (Recommendation #3)	Have an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. (Recommendation 7)	Conduct an assessment of risk of substance abuse, misuse, or addiction (Recommendation 1.1)
Evaluate risk factors for opioid-related harms (Recommendation 8)	Assess suicide risk when considering initiating long term opioid therapy (Recommendation 8)	Evaluate benefit and harms of opioid therapy (Recommendation 1.3)
Review state prescription drug monitoring program (PDMP) data (Recommendation 9)		Informed consent should be obtained and contain goals, expectations, risks, and responsibilities of patient and clinician (Recommendation 2.1)
Use urine drug testing before starting opioid (Recommendation 10)		

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The Ideal *First* Visit

## Opioid Risk Tool (ORT)

Family History of Substance Abuse	Female	Male
Alcohol	1 point	3 points
Illegal Drugs	2 points	3 points
Prescription Drugs	4 points	4 points
Personal History of Substance Abuse	Female	Male
Alcohol	3 points	3 points
Illegal Drugs	4 points	4 points
Prescription Drugs	5 points	5 points
Age (16 to 45 years old)	1 point	1 point
Preadolescent sexual abuse	3 points	0 points
Depression	1 point	1 point
ADD, OCD, Bipolar or Schizophrenia	2 points	2 points

Low Risk: 0-3 points

Moderate Risk 4-7 points

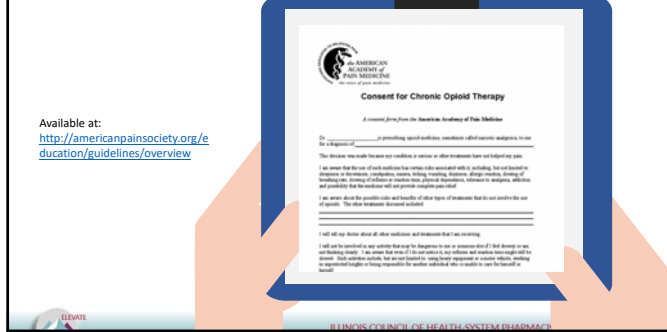
High Risk ≥ 8 points

Pain Med 2005; 6(6): 432-442.

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## Sample Informed Consent




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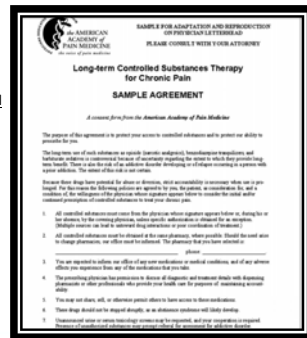
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## Opioid Agreement (or Contract)

### Key features may include:

- Goals of opioid treatment
- Clear explanation that **opioid treatment is a trial** and will be continued or discontinued based on progress toward goals, benefits, and harms/risks
- Specification of 1 physician and 1 pharmacy
- Random urine drug tests
- Office visits at a minimum interval
- Use of pill counts
- Limited prescriptions (i.e. biweekly, monthly)
- Safe storage requirements and disposal
- If medication stolen, must file police report
- Behaviors that constitute non-adherence
- Consequences of non-adherence




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## What are our treatment *goals*?

### CDC #2

"Before starting opioid therapy for chronic pain, clinicians should **establish treatment goals** with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and **function** that outweighs risks to patient safety"

PEG

Pain Average    Enjoyment of Life    General Activity

J Pain 2009; 10 (2): 113-130

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## What are *realistic* goals?

### CDC #3

"Before starting and periodically during opioid therapy, clinicians should discuss with patients **known risks and realistic benefits** of opioid therapy and patient and clinician responsibilities for managing therapy"

**30% - 50%**

Reduction in pain demonstrated in well controlled randomized trials

J Pain 2009; 10 (2): 113-130

Herdon C, et al Principles of Analgesic Use. 7<sup>th</sup> edition.  
Chicago, IL; American Pain Society: 2016, p. 40

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## Guideline Recommendations for *Initiating* Opioid Therapy for Chronic Pain

### CDC #4 #5

### VA #10 #13

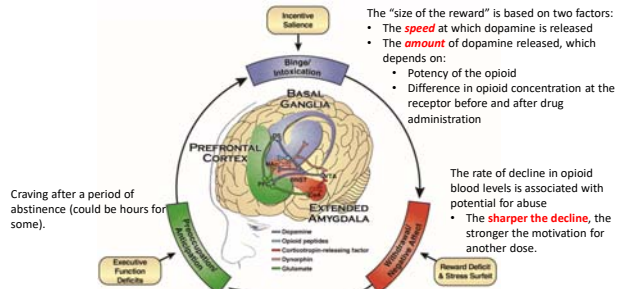
### APS #3

<p>"...prescribe <b>immediate-release opioids</b> instead of extended-release/long-acting (ER/LA) opioids" (<b>Recommendation 4</b>)</p>	<p>"We recommend <b>against</b> prescribing <b>long-acting opioids</b> for acute pain, as an as-needed medication, or on <b>initiation</b> of long-term opioid therapy." (<b>Recommendation 13</b>)</p>	<p>"Clinicians and patients should regard <b>initial treatment with opioids as a therapeutic trial</b> to determine chronic opioid therapy is appropriate." (<b>Recommendation 3.1</b>)</p>
<p>Prescribe the lowest effective dose (<b>Recommendation 5</b>)</p>	<p>Prescribe the lowest effective dose (<b>Recommendation 10</b>)</p>	

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## Consider Impact of Opioid *Pharmacokinetics* on the *Addiction Cycle*



U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. Available at: <https://addiction.surgeongeneral.gov>

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Guideline Recommendations for **Monitoring** Opioid Therapy for Chronic Pain

## CDC #9-10

## VA #7

## APS #5

-Check PDMP at least every 3 months -Consider annual urine drug screen <i>(Recommendation 9 and 10)</i>	<b>Frequency based on risk:</b> <ul style="list-style-type: none"> <li>Ongoing, random urine drug testing (including appropriate confirmatory testing)</li> <li>Checking PDMP</li> <li>Monitoring for overdose potential and suicidality</li> <li>Providing overdose education</li> <li>Prescribing of naloxone <i>(Recommendation 7)</i></li> </ul>	Monitor urine drug screens periodically in patients at high risk of abuse <i>(Recommendation 5.2)</i>
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## Match Monitoring to the Level of Risk of Aberrant Opioid Behaviors

	Low Risk (ORT 0-3)	Moderate Risk (ORT 4-7)	High Risk (ORT ≥ 8)
Patient Visits	Every 1-3 months	Every 2 to 4 weeks	Every 1-2 weeks
Informed Consent or Opioid Agreement	Informed Consent	Opioid Agreement	Opioid Agreement
Random Urine Drug Screen	Initial and Annual	Initial and every 3-6 months	Initial and monthly
Prescription Database Check	Initial and Annual	Initial and every 3 months	Initial and every month
Pill Counts	Annually	Every 6 months	Every 1-3 months
Medication Choice	Adequate analgesia, no restrictions	Limit Rapid Onset Opioids	Limit Rapid-Onset and Short Acting Opioids
Family/Third Party Involvement	Not necessary	Verify patient's adherence and assess for environmental influences	Enlist family member/caregiver to manage medication
Progress Toward Therapeutic Goals	Every visit	Every visit	Every visit
Risk vs. Benefit	Every visit	Every visit	Every visit

Webster L, et al. Avoiding opioid abuse while managing pain. 2007.

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Guideline Recommendations for **'Maximum'** Opioid Dosage in Chronic Pain

## CDC #5, cont.

## VA #11-12

## APS #7

"...Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when <b>increasing dosage to 50 morphine milligram equivalents (MME) or more per day</b> , and should <b>avoid increasing to 90 MME or more per day</b> or carefully <i>justify</i> a decision to titrate dosage to 90 MME or more per day. <i>(Recommendation 5)</i>	"...Risks for overdose and death significantly <b>increase</b> at a range of <b>20-50 mg morphine</b> equivalent daily dose" <i>(Recommendation 11)</i> "We recommend <b>against</b> opioid doses <b>over 90 mg morphine equivalent daily dose</b> for treating chronic pain." At this dose, "evaluate for tapering to reduce dose or discontinue" <i>(Recommendation 12)</i>	"There is <b>no standardized definition for what constitutes a "high" dose</b> . By panel consensus, a reasonable definition for high dose opioid therapy is <b>&gt;200 mg daily of oral morphine (or equivalent)</b> , based on maximum opioid doses studied in randomized trials and average opioid doses observed in observational studies." <i>(Discussion following recommendation 7)</i>
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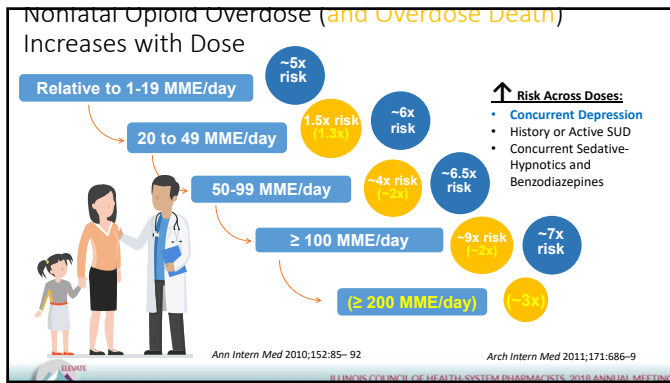
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**Opioid Guidelines *Against* Concurrent Benzodiazepines (and CNS depressants)**

CDC #11	VA #5	APS
<p>"Clinicians should <b>avoid</b> prescribing <b>opioid pain medication and benzodiazepines concurrently</b>" (Recommendation 11)</p> <p><b>Also advises:</b></p> <p>"In addition, the <b>central nervous system depressants (e.g. muscle relaxants, hypnotics)</b> can potentiate central nervous system depression associated with opioids"</p>	<p>"We recommend <b>against</b> the <b>concurrent use of benzodiazepines and opioids</b>" (Recommendation 5)</p> <p><b>Also advises:</b></p> <p>"We suggest <b>not prescribing Z-drugs</b> to patients who are on chronic opioids..."</p>	<p><b>No Recommendation</b></p> <p><b>Advises:</b></p> <p>"Respiratory depression may occur when...opioids are combined with other drugs that are associated with respiratory depression or potentiate opioid-induced respiratory depression (such as benzodiazepines)"</p>

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**Guideline Recommendations for Opioid Therapy for *Acute* Pain**

CDC #6	VA #18	APS
<p>"<b>Three days or less</b> will often be sufficient; more than seven days <b>will rarely be needed.</b>" (Recommendation 6)</p>	<p>If opioids are prescribed, use <b>immediate release</b> opioids and reassess "<b>no later than 3-5 days</b> to determine if adjustments or continuing opioid therapy is indicated."</p> <p>(Recommendation 18)</p>	<p><b>No recommendation</b></p>

**Reduce Opioid *Left-overs*!**

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## Summary

- Limited evidence for efficacy of long term opioid therapy. However, considerable evidence for harm.
- Current guidelines agree that non-opioids/non-pharmacological therapy should be first and foremost in non cancer pain and non end of life pain.
- *Before considering* opioids, evaluate benefits/harms for individual patient and assess risk for opioid related misuse, abuse, and addiction.
- Set *realistic* expectations for opioid therapy, and monitor *function* (as a measure of opioid efficacy but also as a measure of opioid misuse, abuse, or addiction).
- Perform ongoing opioid stewardship activities/monitoring (UDT, PDMP, opioid agreements, pill counts, etc).
- Evaluate "total pain" before opioid initiation, when chemical coping is suspected, with vague descriptions of pain, and when pain increases despite increased analgesic use.
- Take back the opioids and the benzodiazepines (limit prescribing and dispose of leftovers!)

We can **palliate** pain while **avoiding** abuse



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## Additional Slides

For your reference



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## Look for Aberrant Drug-Related Behavior

- **Definition:** behaviors during treatment with a controlled substance that raise concern about addiction, abuse, or diversion

More Serious	Less Serious
Selling prescription drugs	Aggressive complaining about need for higher doses
Forging prescriptions	Drug hoarding
Stealing or borrowing another person's medications	Requesting specific drugs
Injecting oral formulation	Acquiring similar medications from other medical sources
Obtaining prescription drugs from nonmedical sources	Unapproved dose escalation 1-2 times
Concurrent use of illicit drugs	Unapproved use of medication to treat another symptom (i.e. insomnia, anxiety)
Multiple unapproved dose escalations	Reporting effects (i.e. euphoria) not intended by the clinician
Recurrent loss of prescription	Occasional impairment



Pasik SD, Portenay RC, in Holland J, et al: Handbook of Psycho-oncology, 2<sup>nd</sup> ed, 1998; pp 576-586

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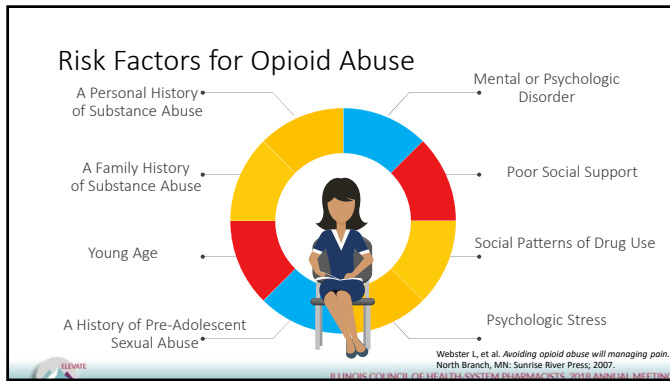
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### Risk Assessment Tools *(perform at initial visit)*

Tool*	# of items	Administered by:
Opioid Risk Tool (ORT)	5	Patient
Screening & Opioid Assessment for Patients with Pain (SOAPP)	24, 14, and 5 (3 versions)	Patient
Diagnosis, Intractability, Risk, & Efficacy Score (DIRE)	7	Clinician

\* Predicts risk of developing opioid-related aberrant behavior, but does NOT diagnosis addiction or opioid use disorder

Webster L, et al. *Avoiding opioid abuse while managing pain*. North Branch, MN: Sunrise River Press; 2007.

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### Urine Drug Tests (UDT): Know Your *Metabolites*

Opioid Prescribed (or using non-medically)	Screening: Opioid Immunoassay	Confirmatory Test with GC/MS (*Metabolite)
Morphine	Positive	Morphine Hydromorphone*
Heroin	Positive	Morphine*
Codeine	Positive	Codeine Morphine* Hydrocodone*
Hydrocodone	Positive/negative (varies among assays)	Hydrocodone Hydromorphone*
Hydromorphone	Positive/negative (varies among assays)	Hydromorphone
Oxycodone	Positive/negative (varies among assays)	Oxycodone Oxymorphone* ?Hydrocodone*
Oxymorphone	Negative	Oxymorphone
Fentanyl	Negative	Fentanyl
Methadone	Negative	Methadone

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FDA News Release

**FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use**

Action to better inform prescribers and protect patients as part of Agency's Opioids Action Plan

For Immediate Release  
August 31, 2016

**Label Change**



<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm>

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Opioid **Tapers** courtesy of the VA/DoD

**Speed of Taper**

Determine speed of taper based on opioid dose, duration of therapy, type of opioid formulation, and risk factors such as co-occurring psychiatric, medical and substance use conditions.

Gradual taper considerations	More rapid taper considerations
Higher opioid dose	Non-adherence to treatment plan
Longer opioid therapy duration – the longer the duration of previous opioid therapy, the longer the taper may take	Escalating high-risk medication-related behaviors
When safety permits, gradual taper is more often tolerated	Drug diversion or illegal activities
Can be completed over several months to years	Risks too high to consider gradual taper
Suggested taper	Suggested taper
5 – 20% every 4 weeks	5 – 20% per week

\*For patients on LOT, consider changing patient's prescription to an equivalent dose of a long-acting opioid (i.e. methadone) then taper methadone accordingly.

[https://www.qmo.amedd.army.mil/OT/OpioidTaperingBooklet\\_FINAL\\_508.pdf](https://www.qmo.amedd.army.mil/OT/OpioidTaperingBooklet_FINAL_508.pdf)

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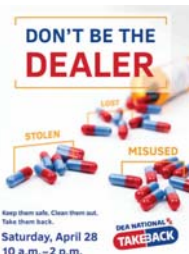
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Opioid **Left-overs**: Take Back the Opioids

- Medication Take Back Programs
  - [https://www.deadiversion.usdoj.gov/drug\\_disposal/takeback/index.html](https://www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html)
  - DEA National Take Back Day: April 28, 2018 - 10AM to 2PM**
    - Cub Foods Parking Lot 1512 S. West Ave Freeport, IL 61032**
- DEA Authorized Collector:
  - <https://apps.deadiversion.usdoj.gov/pubdispsearch/spring/main?execution=s1>
  - OSF Healthcare System 5666 E. State Street, Rockford, IL
  - CVS 110 S. Alpine Rd, Rockford, IL
  - Walgreens 5065 Hononegah Rd, Roscoe, IL
- Dispose in Household Trash
  - Mix in unpalatable substance, place in sealable bag, and put in trash
- Flush in Toilet
- Walmart Dispose Rx



<https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm386187.htm>

[https://www.deadiversion.usdoj.gov/drug\\_disposal/index.html](https://www.deadiversion.usdoj.gov/drug_disposal/index.html)

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### Opioid Disposal: FDA recommendations for *Flushing?*

#### Opioids recommended for disposal by flushing by the FDA:

- All fentanyl products—transmucosal and transdermal
- All buprenorphine products—buccal/sublingual, transdermal (includes combination naloxone products)

Basically all opioid products are on the flush list except:

- Hydrocodone/acetaminophen
- Tramadol
- Codeine products

<https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm576167.htm>




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### Opioid Disposal: the *Walmart method*



SOURCE: DisposeRx  
Frank Rumpas/USA TODAY

<https://www.usatoday.com/story/money/2018/01/17/walmart-takes-opioid-crisis-offering-free-solution-safely-dispose-unused-meds/1039548001/>

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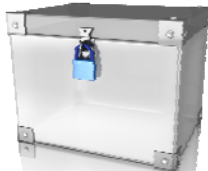
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### Opioid *Safe Storage*

- Remind patients that medications should be stored out reach of children
- In a safe place—preferably locked

Per the CDC, prescribers should “discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient.”



<https://www.end-opioid-epidemic.org/storage-and-disposal/>

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Supplemental Resources (*referenced during talk also*)

**Guidelines (Freely Available):**

- 2009 American Pain Society/American Academy of Pain Medicine Chronic Pain Guideline (samples of informed consent, opioid agreement, ORT in appendix)
  - [http://www.jpain.org/article/S1526-5900\(08\)00831-6/abstract](http://www.jpain.org/article/S1526-5900(08)00831-6/abstract)
- VA/DoD Clinical Practice Guidelines
  - <https://www.healthquality.va.gov/>
- VA/DoD Clinical Practice Guidelines on Pain (includes tapering resource)
  - <https://www.healthquality.va.gov/guidelines/Pain/cot/>
- CDC Guideline for Prescribing Opioids for Chronic Pain
  - <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>

**Books:**

- Herndon CM, et al. Principles of Analgesic Use, 7<sup>th</sup> Ed from the American Pain Society, 2016 (\$38)
  - <http://americanpainsociety.org/education/principles-of-analgesic-use>
- Webster LR. Avoiding Opioid Abuse While Managing Pain, 2007 (\$16)
  - <https://www.amazon.com>

Supplemental Resources

**Webinars:**

- Treating Pain and Avoiding Opioid Use Disorders:
  - <https://pcssnow.org/education-training/treating-chronic-pain-core-curriculum/>
- ER/LA Opioid REMS program from the American Society of Addiction Medicine
  - <https://www.asam.org/education/resources/Opioid-Prescribing>

**Websites:**

- Opioid Information from the FDA (news, approved abuse deterrent formulations, opioid REMS, disposal information)
  - <https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm337066.htm>
- Everything Pain Management! (and sign up for free monthly journal mailing)
  - <https://www.practicalpainmanagement.com/>

## Illinois Prescription Drug Monitoring Program- 2018 Requirements

Mary Lynn Moody BSP Pharm  
Assistant Dean, Business Development  
Clinical Associate Professor  
Department of Pharmacy Practice  
University of Illinois at Chicago College of Pharmacy

## Illinois Prescription Monitoring Program Overview

- The ILPMP receives Controlled Substance prescription data from retail pharmacies daily
- Allows Prescribers and Dispensers to view the historical data for current and prospective patients.



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## What is Public Act 100-0564?<sup>1</sup>

- Amends the current Controlled Substance Act to address concerns of doctor shopping
- Effective January 1, 2018
- Prescribers must register with the Illinois Prescription Monitoring Program
- Should review ILPMP with initial prescription of Schedule II narcotic



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## PMP Registrations

- 64,638 PMP Users (as of March 30th, 2018)
  - 53,548 Prescribers
  - 11,090 Dispensers
- 27,696 registrations since December, 2017



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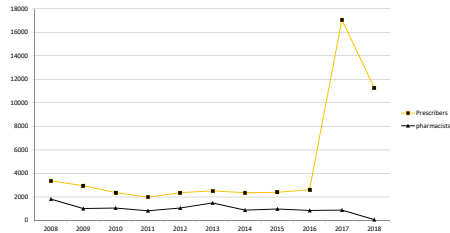
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## Registrations



## PMP Searches by Year

Year	Searches
2013	1,431,538
2014	2,232,916
2015	2,713,137
2016	4,698,186
2017	13,377,213
2018 (Jan-Feb)	7,706,275

## Public Act 100-0564<sup>1</sup>

- Each Prescriber (or their designee) shall document an attempt to access the PMP
- Assess the patient on initial prescription of a Schedule II narcotic (opioid)
- Documentation shall be in the patient's medical record;
  - Exceptions:
    - Oncology Treatment
    - Palliative Care
    - 7-Day or less supply provided by an Emergency Department (treating an acute, traumatic medical condition)

### Public Act 100-0564<sup>1</sup>

- Dispensing pharmacies will receive a copy of the 3:3:1 reports sent to a prescriber
- 3 (or more) pharmacies, and/or 3 (or more) prescribers in a 1 month timeframe
- 786 cases in March 2018



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### Who can access the data contained in the ILPMP?<sup>2</sup>

- Licensed prescribers and dispensers (pharmacists) of controlled substances **AND THEIR DESIGNEES** can view the ILPMP data for current and prospective patients only
- Law enforcement officers are allowed indirect access to prescription data during an active investigation



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### How many designees can I have and who can they be?<sup>3</sup>

- Prescribers or dispensers may have up to 3 designees
- Only those listed below can serve as an authorized designee
  - registered nurse
  - licensed practical nurse
  - pharmacy technician
  - student pharmacist
  - certified medical assistant
- You must register your designees and agree to the terms and conditions



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### Designees<sup>3</sup>

- Each designee shall have an individual account that must be linked to the prescriber or dispenser.
- PMP staff shall verify the following information about each designee:
  - license/certification number
  - employer's phone number and address
  - work email address
  - If no work email is available, PMP staff shall contact the prescriber or dispenser to verify the designee
- PMP shall send out a notice for the prescriber or dispenser to ensure continued employment of their designees
- If the designee is no longer employed with the prescriber or dispenser, the prescriber or dispenser shall terminate the designee's access to the PMP by locking the designee's account or by notifying the PMP that the designee's account should be locked.



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### Can I consult with prescribers and other dispensers listed on the ILPMP without patient authorization?<sup>3</sup>

- According to HIPAA, this type of consultation is permitted because consultation is within the HIPAA definition of "treatment"



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### Why can't I find prescriptions that I know were filled?<sup>3</sup>

There could be several reasons for this:

- Dispensing pharmacy is not properly reporting their prescription data
- Search strategy-Names are ambiguous



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### Example of ambiguous name

- A prescription written by a prescriber for a patient with the first name of "Jennifer" but the pharmacy filled it as "Jenifer"
- Enter the first few defining letters of the name up to the point where ambiguity may begin. For example, enter "Jen" as the patient's first name

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### PMPnow<sup>4</sup>

- Allows seamless integration of PMP Data into the Electronic Health Record System
- No need to logon to PMP website
- 31 Connections-671 sites in Illinois, Missouri and Iowa
  - hospitals
  - clinics
  - pain clinics
  - FQHC

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### References

1. Illinois General Assembly. Public Act 100-0564. <http://www.ilga.gov/legislation/publicacts/fulltext.asp?Name=100-0564>. Accessed August 8, 2018.
2. Joint Committee on Administrative Rules. Administrative Code. Section 2080.210 Access to the Prescription Information Library (PIL). <http://www.ilga.gov/commission/icar/admincode/077/07702080000210OR.html>. Accessed August 8, 2018.
3. Illinois Prescription Monitoring Program. <https://www.ilpmp.org/QandA.php>. Accessed August 8, 2018.
4. Illinois Department of Human Services. PMPnow Illinois prescription monitoring program-DHS 4198. <http://www.dhs.state.il.us/page.aspx?item=97344>. Accessed August 8, 2018.

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## Improving Opioid Safety with Behavioral Economic Theory

**Adam J. Bursua, PharmD, BCPS**  
Medication Safety and Quality Coordinator - UI Health Clinical  
Assistant Professor – UIC College of Pharmacy



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### Solutions to the Opioid Crisis

- Awareness campaigns
- Clinical care guidelines
- Prescribers education
- Utilizing PMPs
- Screening for and treating opioid use disorders

- All of these interventions rely on traditional theories of decision making behavior:
  - Rationale operators making rational choices



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### The “Nudge” Theory of Decision Making

- Traditional economic theory:
  - Rational beings making rational decisions
- “Nudge theory”:
  - People often choose what is easiest over what is wisest



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## What is a “Nudge”?

- A strategy to alter “people’s behavior in a predictable way without forbidding any options or significantly changing their economic incentives.”
- “Nudges are not mandates. Nudges do not impose material costs but instead alter the underlying choice architecture”

-Thaler & Sunstein



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## A Different Crisis

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- Fueled by switch to defined contribution plans from defined benefit
- Workers don’t enroll in 401k programs at high enough rates
- Even when they do enroll, they don’t save enough



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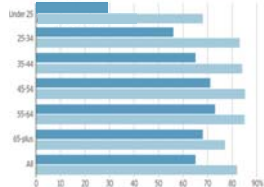
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## Nudge Theory - Applied

### Little Nudge, Big Impact

Participation rates by age for Vanguard defined-contribution retirement plans



Source: Vanguard Group data for 2017 on about 400 plans and 385,000 participants and eligible nonparticipants.

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## Nudge Theory - Applied




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## Nudge Theory - Applied

Image removed due to copyright

36% higher vaccination rates for E-mail 1 group

### • Free flu shots are being offered

- Email 1:
  - Your appointment for influenza vaccination has been scheduled for 10/01/2018 at 2pm
    - To change or modify your appointment, click here
- Email 2:
  - To schedule an appointment for your vaccine click here

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## What About Opioid Prescribing?

"Rational beings making rational decisions."

"People often choose what is easiest over what is wisest"

### Traditional solutions

Develop guidelines  
Educate prescribers  
Awareness campaign  
Academic detailing

### Nudge solution

Modify choice architecture to nudge prescribers toward the desired behavior

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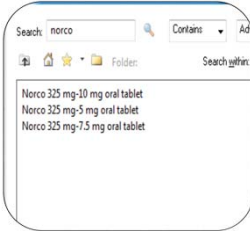
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## Opioid Prescribing Choice Architecture

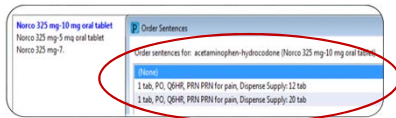


- 1 tab, po, q4H, prn for pain
- 1 tab, po, q6H, prn for pain
- 2 tab, po, q4H, prn for pain
- 2 tab, po, q6H, prn for pain

## Nudging Theory - Applied

- 1 tab, po, q4H, prn for pain
- 1 tab, po, q6H, prn for pain
- 2 tab, po, q4H, prn for pain
- 2 tab, po, q6H, prn for pain

**1 tab, Q6, PRN, Disp qty 12 tab**  
**1 tab, Q6, PRN, Disp qty 20 tab**



### Before

Q4 hour orders = 33.1%  
 2 tab orders = 3.85%  
 3 day supply = 5.79%

Total tablets  
 written/month  
 = 88380

### After

Q4 hour orders = 11.7%  
 2 tab orders = 2.46%  
 3 day supply = 11.6%

Total tablets  
 written/month  
 = 67323

**On average ~ 21,000 thousand fewer tablets  
 prescribed each month**

## Targeting the system

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## Target the System




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## Medication Event Case Report

A patient who was receiving an opioid for pain was found unable to be aroused. Naloxone was given, and the patient was successfully rescued.

### Progress notes:

"Pain: Morphine 2mg Q2 as needed"

### Order:

Morphine, IV Push, 2mg, Q2 hours

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## Nudged...the wrong way

- During the RCA, it was noted that one of the order sentence defaults was:

Morphine, IV Push, 2mg, Q2 hours



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## Use Default Selections to Your Advantage

- People tend to exhibit inertia
- Expectation that defaults are screened by experts
- Defaults can then serve as reference points
- Defaults normalize behavior



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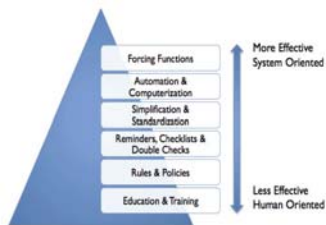
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## Target the System



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## Target the System




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## Learning From Failure

Using Naloxone Utilization Data to Identify Improvement Opportunities

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## Naloxone Case Review

- Each case of naloxone administration is analyzed
  - Patient information
    - Opioid risk factors
    - Encounter characteristics (e.g., surgery vs. medical)
  - Medication information
    - Opioid(s) used
    - Concomitant sedatives

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## Common Themes

- Morphine use in renal dysfunction
- Opioid use for mild pain indications
- Substandard sedation assessment documentation

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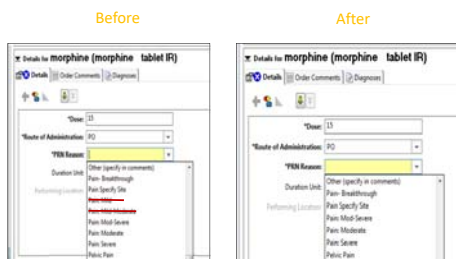
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## Modifying Choice Architecture




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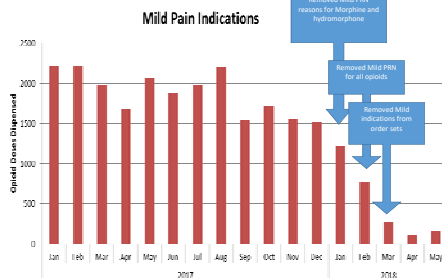
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## Opioid Use for Mild Pain




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## Target the System

The screenshot shows two side-by-side views of a clinical system interface. The 'Before' view on the left shows a patient record for 'Sedation Scale' with a note: 'There is no requirement for sedation scale documentation.' The 'After' view on the right shows the same patient record, but with a new requirement: 'Sedation score (sedation scale) will now be a required documentation field.' A red box highlights the 'Sedation Scale' field in the 'After' view, indicating it is now a required field.

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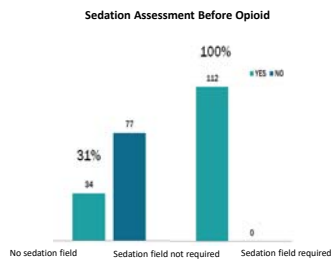
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## Target the System




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## Questions?

Contact:  
Adam Bursua, abursu1@uic.edu

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Panel Discussion

## The Opioid Crisis: EFFECTIVE STRATEGIES TO TURN THE TIDE

Saturday, September 15, 2018  
1:00pm-3:00pm  
ICHP Annual Meeting  
Crystal Room - Drury Lane Conference Center  
Oakbrook Terrace, IL

  
 Adam Bursa,  
PharmD, BCPS

  
 Annette Hays,  
PharmD, BCPS

  
 Mary Lynn  
Moody,  
BSPharm

  
 Laura Meyer-Juncos,  
PharmD, BCPS,  
CPE

  
 Kevin O. Rynn,  
PharmD, FCCP,  
DABAT

  
 Christopher  
Schriever, MS,  
PharmD

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### Any ideas??? What's our plan?

- Numerous local members convened to determine ideal location to initiate strategies to combat current opioid epidemic
- Participants identified a number of clinic-wide approaches to address the issue
- Region-wide tactics were developed attempting to tackle problem from a community standpoint
- End result is to provide multiple, adaptable approaches to control current epidemic

(Image removed due to copyright)

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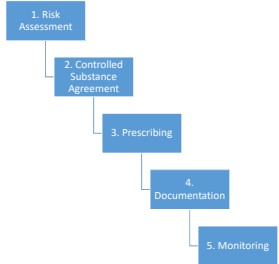
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### UI Health L.P. Johnson Family Health Center

- Family Medicine Clinic**
  - 21 resident physician
  - 10 attending physicians
  - 4 registered nurses
  - 1 pharmacist
- Controlled Substance Policy**
  - Five key components
  - Personnel accountability
  - Pre and post assessments



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graph TD
    A[1. Risk Assessment] --> B[2. Controlled Substance Agreement]
    B --> C[3. Prescribing]
    C --> D[4. Documentation]
    D --> E[5. Monitoring]
          
```

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### Regional Strategies

- Single-day, interprofessional Opioid Summit held at the Rockford Campus
- UIC drug take-back partnership with Keep Northern Illinois Beautiful
- Improved relationship with Winnebago County Health Department and alignment of initiatives
- Development of student-driven opioid crisis advertising and education
- Continuing education programs





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Rank the top two opioid crisis strategies you would like to explore further (must go through [pollev.com/ichp](https://pollev.com/ichp) to respond)

Improving access to naloxone for at-risk patients	
Improving patient education about opioid risks	
Changing opioid prescribing behavior for pain	
Better utilization of PMP data	
Tapering chronic pain patients off of opioids	
Increased utilization of medication assisted therapy for patients with opioid dependence	



Start the presentation to see live content. Still no live content? reload the app or get help at [pollev.com/app](https://pollev.com/app)

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### Questions/Discussion



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# The Opioid Crisis: Effective Strategies to Turn the Tide

Post Test Questions pertain to the following case:

Jane is a 42 year old female with chronic back pain from a motor vehicle accident 5 years ago and painful diabetic neuropathy. You are seeing her for the first time as her PCP retired.

- Comorbid conditions include anxiety, depression, diabetes, insomnia, current smoker of 1 pack/day, and a remote history of alcohol use disorder
- Denies history of sexual or domestic abuse
- Family history of alcoholism
- Currently going through divorce from husband of 15 years
- Pertinent prescriptions include:
  - Oxycodone/acetaminophen 5 mg/325 mg 1 tablet q 4 hours as needed for pain
  - Gabapentin 300 mg TID
  - Lorazepam 1 mg TID
  - Cyclobenzaprine 5 mg BID
  - Zolpidem 5mg nightly
- Review of the prescription drug monitoring program reveals several early refills over the last three months.
- Today, she reports increasing diffuse pain that does not appear consistent with physical examination
- She reports that taking 2 tablets 5 times daily has really helped her pain, and she is wondering if her prescription could be increased

1. *Which term best describes Jane's recent oxycodone/acetaminophen use?*

- A. Tolerance
- B. Addiction
- C. Pseudoaddiction
- D. Chemical Coping
- E. Diversion

2. *How would you stratify Jane's risk of aberrant opioid taking behavior (using the Opioid Risk Tool)?*

- A. Very Low
- B. Low
- C. Moderate
- D. High
- E. Very High

**3. Which of the following can increase Jane's risk of respiratory depression from opioids?**

- A. Lorazepam**
- B. Cyclobenzaprine**
- C. Zolpidem**
- D. Gabapentin**
- E. All of the above**

# How to Build Your Professional Network

Chris Crank, PharmD, MS, BCPS AQ ID & Jen Phillips, PharmD, BCPS, FCCP, FASHP  
September 15, 2018

## INTRODUCTION

- Most jobs are discovered and achieved via “word of mouth”
- Networking is building relationships *with people who can help build you!*
- Benefits of networking
  - Enhance your reputation
  - Stay up-to-date on emerging trends
  - Find mentor(s), collaborators, sounding boards
  - Introduce you to others
  - Find opportunities

### Step 1: Identify Who You Want in Your Network

- What are you looking for?
- Diversify: mentor, coach, “trendsetter”, idealist, realist, visionary, “cheerleader”, “devil’s advocate”
- Expand outward (# of people in your network) and inward (quality of relationships with contacts)

### Step 2: Decide Where to Start

- Get involved with organizations
  - Volunteer for committees, leadership roles
  - Attend networking events, socials, grass roots campaigns
- Be Present on Social Media
  - Choose platform you are comfortable with
  - Don’t be a “passive” member
- Collaborate with new people on projects/research
- Grow your network up (supervisors or more experienced), down (supervisees or less experienced), and sideways (those with the same experience/job level as you)

### Step 3: Develop Your “Elevator Speech” for Face-to-Face Meetings

- 1 minute or less
- Clear, concise, and compelling
- Includes background, key achievements, and future plans
- Hint: avoid too much alcohol at in-person social/professional gatherings

### Step 4: Learn How to Talk to People

- Learn how to use “small talk” as a conversation opener
- Discuss common problems everyone is facing
- Discuss topics outside of pharmacy, too!
- Find a single person or small group



**Step 5: Build Your Reputation**

- Be PRESENT
  - Make meaningful contributions in your role
    - Voice your opinion, speak your mind (thoughtfully)
    - Volunteer for tasks and finish in a timely manner
- Find a mentor/sponsor
  - Helps keep you in the loop of potential opportunities
  - Helps promote your skills/abilities to others
- Let others know of your (potential) long-term plans
  - Succession planning usually starts years in advance

**Step 6: Pay it Forward**

- Identify a promising rising star and help guide them through steps 1-5!

**References**

Gumbus A, Lussier RN. Career development: enhancing your networking skills. *Clin Leadersh Manag Rev.* 2003;17(1):16-20.

## The Residency Showcase & Preparing for the Interview

Nora B Flint, Pharm.D., BCPS, FASHP  
Director, PGY1 Residency Program  
Rush University Medical Center  
Chicago, IL  
September 2018



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## The Residency Showcase

- Do your homework, know what programs will be there and those that you want to talk to
- You have only one chance to make a good first impression
- Skip the busy programs and go to the back of the room to the less busy ones first; manage your time
  - Go to the in-state program showcases and skip them at the national showcases
  - Focus on out-of-state program showcases at the midyear
- Talk to preceptors/program directors AND residents



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## The Residency Showcase

- Don't monopolize anyone
- Don't schmooze
- Double check due dates for applications (ASHP directory may not be updated)
- Take notes afterwards so you will remember
  - Develop spreadsheet of programs, things you like/don't like
  - Be organized (great training for your residency)



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### What Do You Want To Know?

- Think about what information that will help you distinguish one program you would prefer over another one
- Think about how can you ask your questions professionally?
  - How many hours a day will I have to be at the hospital? ☹️ ....OR
  - What is a typical resident's day like? 😊



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### What Do You Want To Know?

- Do you have specific areas that you want to practice in?
  - Research the programs for rotations offered, inpatient vs outpatient opportunities
- Do you have specific skills that you want to become proficient in?
- Do you want a small or large residency class?
- Self-assess what you want/need for your career in order to best prepare for interactions with programs

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### Getting Ready for the Interview

*(it helps for the showcase, too)*

- Research the programs you interviewing with
  - Hospital websites
  - ASHP directory
  - Google
  - Your network
    - Talk to former students from your school that went onto residency programs you are interested in



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## What Do You Want To Do After The Residency?

- Be as specific as you can
  - You have the privilege of changing your mind during your residency; no one will judge you
- Being a "clinical pharmacist" is not an answer; what does that mean?
- Be ready to articulate what you see yourself doing and why it appeals to you
- Don't sound rehearsed – go over your answers beforehand with mentor or friend
- You have only one chance to make a good first impression (sound familiar?)



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## Questions to be ready for

- What was your best patient care intervention and why?
- When did you feel you had the best interaction with another healthcare provider and why?
- When did you fail making an intervention and what did you learn from it?
  - Develop a "story bank"
- Why should we pick you?
- Why are you looking at us?



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## What Not To Ask

- Don't ask questions that are easily found on a program's website, or in printed material
- Don't ask a program to change what they can offer just for your interests – it's not that easy!
- Never ask about salary/stipend/pay
- Never ask about vacation; it sends the wrong message



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## Follow up

- Thank you notes
  - If you can add specifics from the interview dialogue to the note, that hits home
- Hand-written is special
- If email is necessary, take note that your font is consistent; if it's not, that's a sure sign of cut & paste and now I'm not feeling so special.....



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## PGY-1 Residency Training Programs: What are my options?

Susan R. Winkler, PharmD, BCPS, FCCP  
Professor and Chair, Department of Pharmacy Practice  
PGY-1 College Liaison, Jewel-Osco Pharmacy  
Midwestern University  
Chicago College of Pharmacy

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## PGY-1 Programs

- Separate accreditation standards for:
  - Pharmacy
    - Most common
  - Community
  - Managed Care
- Even programs following the same accreditation standard can have a different look, feel

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## PGY-1 Programs

- Different Settings
  - Academic Medical Centers
  - Community Hospitals
  - Acute Care vs. Ambulatory Care
  - College-based
- Different Patient Populations
  - Ambulatory Care
  - Pediatric Hospital
  - Veterans Affairs Medical Center

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### PGY-1 Pharmacy: Two Different Programs

#### Academic Health-Center Based

- Orientation
- Cardiology
- Internal Medicine
- Administration
- Drug Information
- Transplant
- Infectious Diseases
- Research/Project Month
- Internal Medicine II
- Ambulatory Care
- Pediatrics
- Longitudinal: Service/Staffing

#### College-based: Teaching & Ambulatory Care

- Amb Care I: Anticoagulation
  - Underserved Population
- Internal Medicine Inpatient
- Amb Care II: Diabetes
- Amb Care III: Medical Home
- Amb Care IV: Pulmonary
  - VA Setting
  - Community
- Community Practice
  - Service/Staffing/Management
- Longitudinal: Teaching/Precepting, Academia, Project

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### PGY-1 Program: Day in the Life

#### Patient Care

- Morning Rounds
  - Work rounds
  - Teaching rounds
- Patient Appointments
- Medication Reconciliation
- Antibiotic Stewardship

#### Other

- Medication Safety Meeting
- Topic Discussions with Students
- Project Meeting with Mentor
  - Data collection
- Staffing

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### PGY-1 Community

- Accredited by ASHP in partnership with APhA
- Various models for operation of residencies:
  - College of pharmacy and community pharmacy partnerships
  - Independent programs through colleges of pharmacy with their own pharmacies
  - Independent programs through community pharmacies or chain corporations

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### PGY-1 Community: Day in the Life

- Corporate experiences in leadership, practice management
- Development of business plan and implementation of pharmacy service
- Community Pharmacy Operations
- Community Pharmacy Clinical Services
- Ambulatory Clinic experiences
- Work within collaborative practice models
- Academic experiences
  - Didactic teaching
  - Practice-based research project
  - Grand Rounds

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### All PGY-1 Programs

- Service Commitment
  - Staffing
    - Responsibilities
    - Time: How much? When? (i.e., weekends, evenings, on-call)
- Teaching Commitment
  - Is this something you want?
  - Is there teaching-related training?
- Program Size

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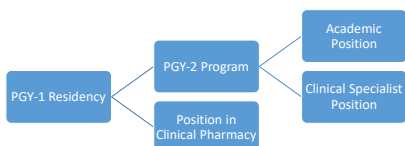
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### What next?




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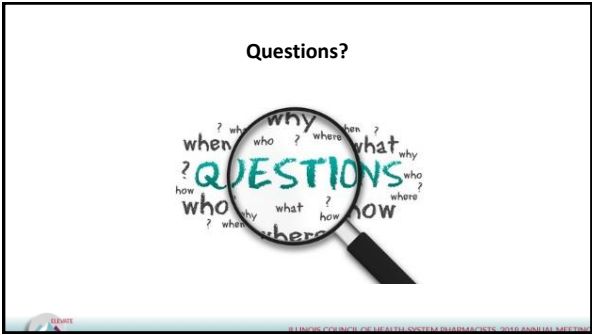
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