CEimpact
PHARMACY EDUCATION

GameChangers: A Year in Review Part 1

Geoffrey C. Wall, PharmD, FCCP, BCPS

1

Faculty

Geoffrey C. Wall, PharmD, FCCP, BCPS

Professor of Pharmacy Practice, Drake University

Internal Medicine Clinical Pharmacist

Iowa Methodist Medical Center

Des Moines, IA

2

CEimpact 3

Disclosure

- Geoff Wall reports the following:
  - Speaker's bureau member for Janssen and La Jolla Pharmaceuticals
  - Off-label use of medication will be discussed during this presentation

3

CEimpact 4

Pharmacist Learning Objectives

Upon successful completion of this course, pharmacists should be able to:

- Classify "Gamechangers" by how they affect practice settings.
- Discuss the selection of each "Gamechanger" topic and how they will impact the provision of patient care.
- Describe possible solutions to clinical problems listed throughout the presentation.
- Assess the clinical trials used to support the content for this presentation.
- Apply the information presented to influence patient care and outcomes at your specific practice site.

4

CEimpact 5

Pharmacy Technician Learning Objectives

Upon successful completion of this course, pharmacy technicians should be able to:

- Classify "Gamechangers" by how they affect practice settings.
- Discuss the selection of a "Gamechanger" topic and how it will impact the provision of patient care.
- Describe opportunities for the advancement of pharmacy technician roles based on information presented.
- Identify the clinical trials used to support the content for this presentation.
- Apply the information presented to influence patient care and at your specific practice site.

5

CEimpact 6

What are Gamechangers?

- Facets of clinical medicine that directly impact the everyday practice of the majority of “boots on the ground” pharmacists
- Some Gamechangers are specific to practice site settings
  - e.g., IV drug shortages or oral blockbuster drug goes generic
- Others are more general in scope
  - e.g., Affordable Care Act changes or landmark study published

6

Examples of Gamechangers

- New, first-in-class drug released
- Vanguard or seminal study published
- Wide-impact practice guidelines
- Reported ADRs of widely used medications
- FDA regulations/warnings
- New or changing laws/policies
- Economic changes

7

Gamechanger #1

SGLT2 Drugs for Heart Failure:
The "statins" of the 21st century

8

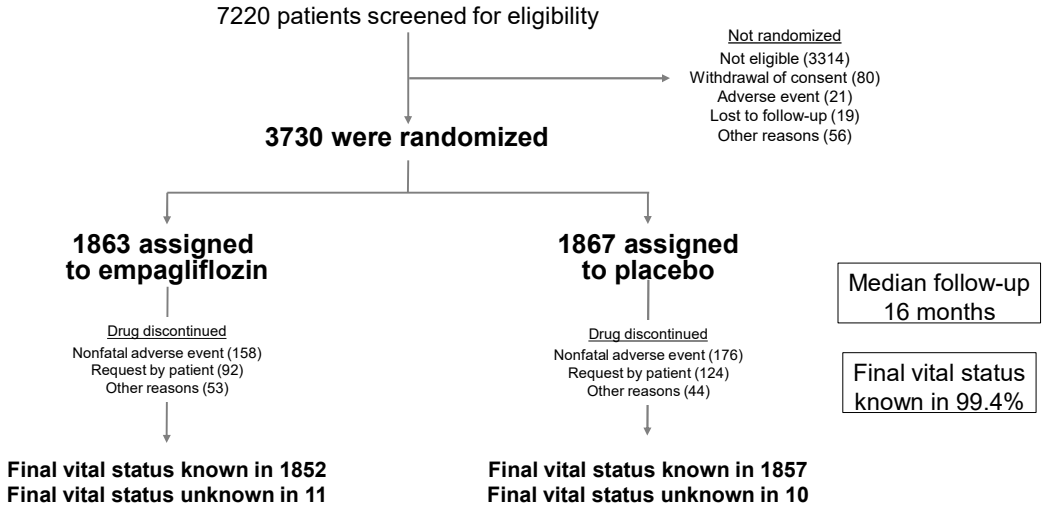
EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Packer M, et al. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

9

EMPEROR-Reduced: Patient Disposition



CEimpact

10

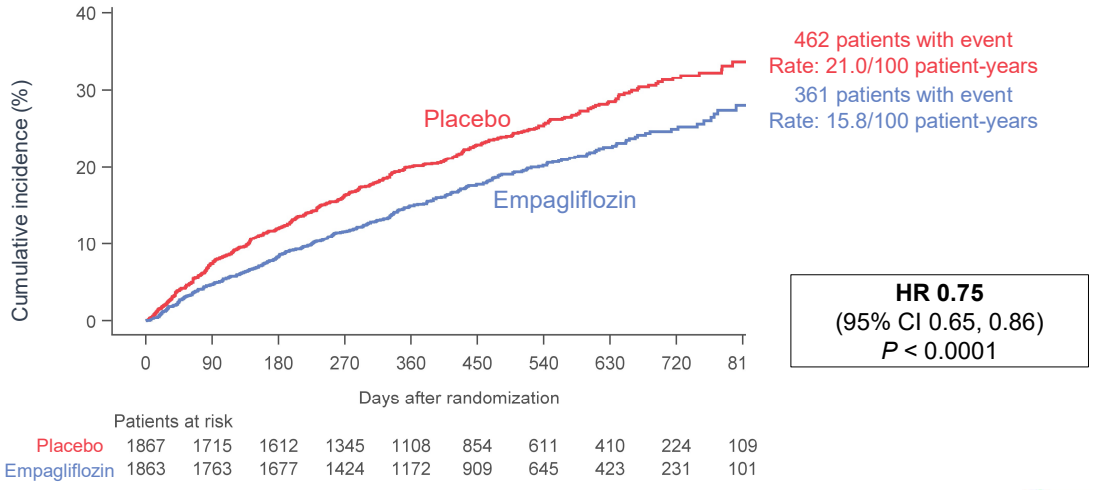
Baseline Characteristics

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	**Placebo (n=1867)**	**Dapagliflozin (n=2373)**
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	**27.7 ± 6.0 (72% ≤30%)**	**27.2 ± 6.1 (75% ≤30%)**	**31.2±6.7**
NT-proBNP (median, IQR), pg/mL	**1887 (1077, 3429) (79% ≥1000)**	**1926 (1153, 3525) (80% ≥1000)**	**1428 (857-2655)**
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	1124 (47.4)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m²)	**61.8 ± 21.7**	**62.2 ± 21.5**	**66.0 ± 19.6**
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	**340 (18.3)**	**387 (20.7)**	**250 (10.5)**
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

CEimpact

11

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)

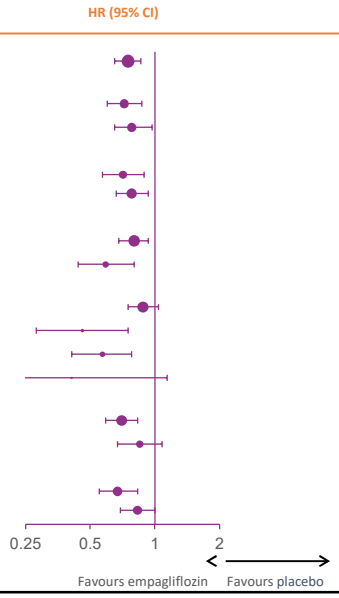


CEimpact

12

EMPEROR-Reduced: Primary Endpoint Subgroups

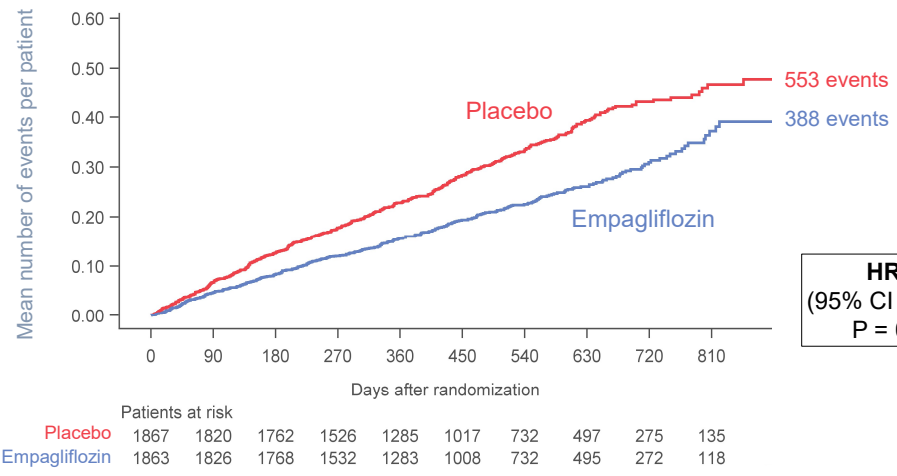
	Empagliflozin n with event/N analysed	Placebo n with event/N analysed	Hazard ratio (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Baseline diabetes status			
Diabetic	200/927	265/929	0.72 (0.60, 0.87)
Non-diabetic	161/936	197/938	0.78 (0.64, 0.97)
Age, years			
<65	128/675	193/740	0.71 (0.57, 0.89)
≥65	233/1188	269/1127	0.78 (0.66, 0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68, 0.93)
Female	67/437	109/456	0.59 (0.44, 0.80)
Race			
White	264/1325	289/1304	0.88 (0.75, 1.04)
Black/African-American	24/123	48/134	0.46 (0.28, 0.75)
Asian	62/337	99/335	0.57 (0.41, 0.78)
Other	5/51	14/63	0.41 (0.15, 1.14)
Body mass index (kg/m²)			
<30	226/1263	322/1300	0.70 (0.59, 0.83)
≥30	135/600	140/567	0.85 (0.67, 1.08
Baseline eGFR (CKD-EPI), ml/min/1.73 m²			
<60	159/969	224/960	0.67 (0.55, 0.83)
≥60	202/893	237/906	0.83 (0.69, 1.00)



CEimpact

13

EMPEROR-Reduced: Total Hospitalizations for Heart Failure (First and Recurrent) — Hierarchical Endpoint #2

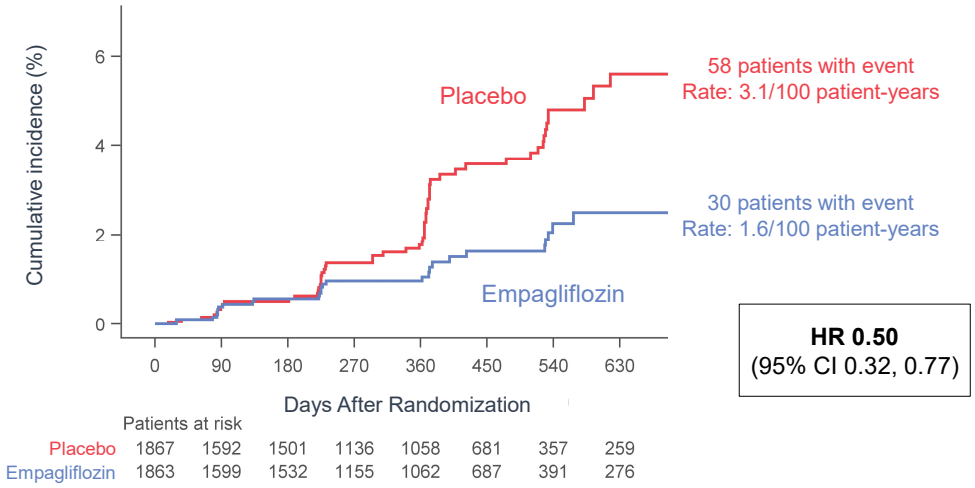


HR 0.70
(95% CI 0.58, 0.85)
P = 0.0003

CEimpact

14

EMPEROR-Reduced: Composite Renal Endpoint



HR 0.50
(95% CI 0.32, 0.77)

CEimpact

15

EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

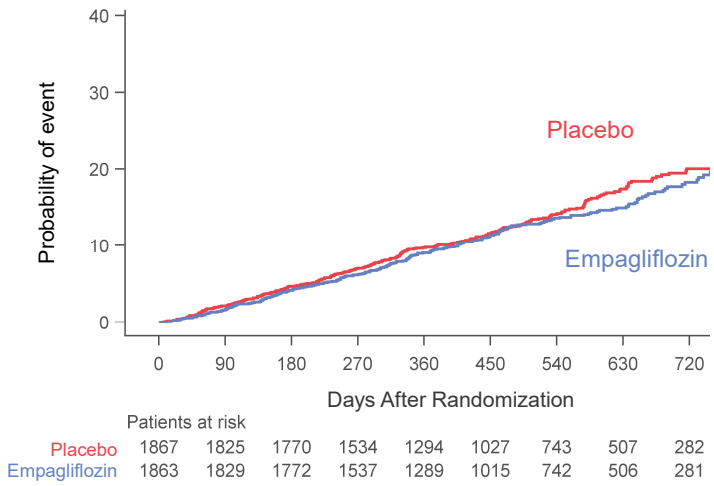
	Primary Endpoint Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	First Secondary Endpoint Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	Second Secondary Endpoint Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

CEimpact

16

EMPEROR-Reduced: All-Cause Mortality



266 patients with event
Rate: 10.7/100 patient-years

249 patients with event
Rate: 10.1/100 patient-years

HR 0.92
(95% CI 0.77, 1.10)

CEimpact

17

Trials in Heart Failure and a Reduced Ejection Fraction (With or Without Diabetes)		
	DAPA-HF (dapagliflozin)	**EMPEROR-Reduced (empagliflozin)**
Cardiovascular death or hospitalization for heart failure	0.75 (0.65 – 0.85) [877 events]	0.75 (0.65 – 0.86) [823 events]
First hospitalization for heart failure	0.70 (0.59 – 0.83) [549 events]	0.69 (0.59 – 0.81) [588 events]
Renal composite endpoint	0.71 (0.44 – 1.16) [67 events]	0.50 (0.32 – 0.77) [88 events]
Cardiovascular death	0.82 (0.69 – 0.98) [500 events]	0.92 (0.75 – 1.12) [389 events]
Trials in Type 2 Diabetes (With or Without Heart Failure)		
	DECLARE-TIMI58 (dapagliflozin)	**EMPA-REG OUTCOME (empagliflozin)**
Cardiovascular death or hospitalization for heart failure	0.83 (0.73 – 0.95) [913 events]	0.66 (0.55 – 0.79) [463 events]
First hospitalization for heart failure	0.73 (0.61 – 0.88) [498 events]	0·65 (0·50 – 0·85) [221 events]
Renal composite endpoint	**0.53 (0·43 – 0·66)** [365 events]	**0·54 (0·40 – 0·75)** [152 events]
Cardiovascular death in patients with prior myocardial infarction	**0.92 (0.61 – 1.23)** [183 events]	**0.59 (0.44 – 0.79)** [183 events]

CEimpact

18

Conclusions

- In patients with chronic heart failure and a reduced ejection fraction, EMPEROR-Reduced achieved all three endpoints prespecified as key outcomes by hierarchical testing, each with a $P < 0.001$.
- The 25% decrease in the risk of the composite of cardiovascular death and heart failure hospitalization observed in EMPEROR-Reduced was identical to that seen in DAPA-HF. Empagliflozin reduced the total number of hospitalizations for heart failure and slowed the rate of progression of renal disease.
- Although the effect on cardiovascular death in EMPEROR-Reduced was smaller than that seen in DAPA-HF, the reverse was true when the effects of dapagliflozin and empagliflozin on cardiovascular death were assessed in comparable patients in trials of type 2 diabetes. Accordingly, the effects of these drugs on survival is characterized by significant heterogeneity.
- Taken together, we believe that the concordant results of DAPA-HF and EMPEROR-Reduced should be sufficient to establish SGLT2 inhibitors as a new standard of care for patients with heart failure and a reduced ejection fraction.

19

EMPEROR-Preserved—YES even in HFpEF!!

- Randomized, double blind, parallel-group, placebo-controlled, event driven trial
- Inc: > 18 years , who had NYHA Class II-IV symptoms and a left ventricular ejection fraction of more than 40% and a NT-proBNP level of more than 300 pg/mL
- Exc: MI in last 90 days, Recent CHF hospitalization, severe valvular heart disease, AF with resting heart rate > 110, severe HTN
- Placebo or empagliflozin, 10 mg per day, in addition to usual therapy. Randomization was performed with a permuted block design and was stratified by geographic region, diabetes status, estimated glomerular filtration rate (eGFR) < or > 60 mL/min and EF of less than 50% or 50% or more

Packer M, et al .Circulation. 2021 Oct 19;144(16):1284-1294. doi: 10.1161/CIRCULATIONAHA.121.056824. accessed 11/10/21

20

Baseline Characteristics

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N = 2997)	Placebo (N = 2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m²	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m² — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

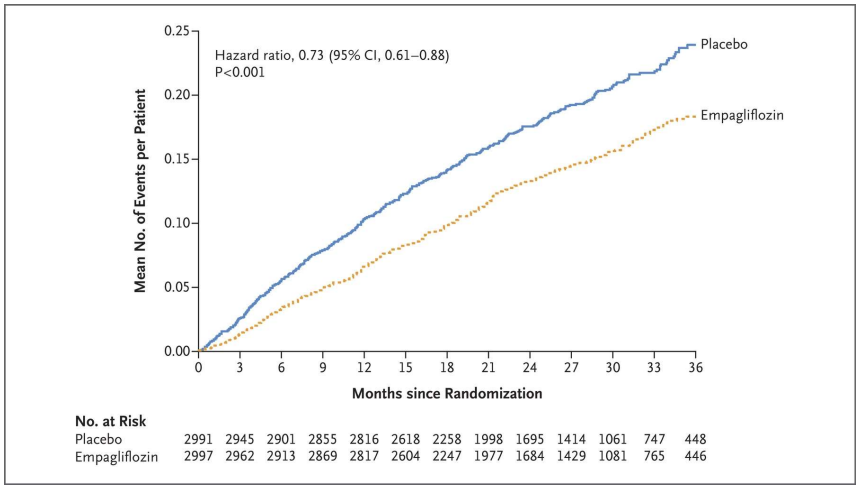
- Most patients are in Class II CHF
- About 50% of the patients have DM

Packer M, et al .Circulation. 2021 Oct 19;144(16):1284-1294. doi: 10.1161/CIRCULATIONAHA.121.056824. accessed 11/10/21

CEimpact

21

HF Hospitalizations



CEimpact

22

Bottom Line

- SGLT2 drugs have shown conclusively to improve outcomes in HFrEF and HFpEF with or without patients also having DM
- Improves symptoms, hospitalizations, and CV death
- Slows concomitant renal disease
- BUT
  - Watch out for dehydration, especially in those already on loop diuretics – practitioners should reduce dose or consider stopping these drugs when initiating SGLT2s
  - Euglycemic DKA
  - Cost (of course)

23

Gamechanger #2

POCT and "test and treat" for Community Pharmacy

24

Introduction

- Point of care testing (POCT) has become routine in many community pharmacies - almost exclusively for screening purposes or monitoring therapies:
  - Blood glucose readings
  - A1C
  - Cholesterol levels
  - INR in patients on warfarin
- Update has largely been dependent on staffing and, of course, reimbursement
- What about ID related POCT?

25

Opportunities for Point-of-Care Testing

- Influenza - causes 12,000-50,000 deaths annually in the United States
  - Rapid testing for influenza A and B allows for accurate and timely treatment, patients only have a 48-hour window to receive critical antiviral therapy
    - Tests available by: BD*, Quidel*, Alere
- Strep A - Only 10-15% of adults with acute pharyngitis (a sore throat) test positive for strep; yet up to 75% are prescribed antibiotics
  - Most pharyngitis cases are viral and self-limiting in nature and could be symptomatically treated with OTC products. Combating antibiotic resistance should be a priority for all pharmacy teams
    - Tests available by: BD*, Quidel*, Roche
- COVID – popularity will increase as new oral therapeutics hit the market

https://ncpa.org/point-care-testing-poct. Accessed 10/5/21

26

Chronic Infectious Diseases

- HIV - there are an estimated 200,000 undiagnosed HIV-infected individuals in the United States; it is recommended that anyone who is sexually active or engages in high-risk behavior consider screening
  - Obvious issues surrounding confidentiality and referral
    - Tests available by: OraSure, BioLytical
- Hepatitis C - 3.5 million people are infected with HCV in the United States and about half are unaware they have the virus; it is recommended that all persons born between 1945 and 1965 be screened
  - Recommended by USPSTF in adults aged 18 to 79 years

https://ncpa.org/point-care-testing-poct. Accessed 10/5/21

27

Example of Criteria of Treat and Test (KY)

CRITERIA
Pharmacists authorized to initiate the dispensing of antiviral therapy to treat acute influenza infection will treat individuals according to annual guidance from the CDC.[1]

Inclusion criteria:
Any individual who presents to the pharmacy during influenza season, when known influenza viruses are circulating in the community, and meets **ALL** of the following criteria:
- Age 5 years or older (with consent of a parent/guardian if < 18 years old)
- Complaint of **ANY** sign/symptom consistent with influenza (fever, myalgia, headache, malaise, nonproductive cough, sore throat, rhinitis)
- Reported symptom onset < 48 hours before time of presentation
- Positive influenza virus result via CLIA-waived point-of-care RIDT or PCR

Exclusion criteria:
Any individual who meets **any** of the following criteria:
- Age < 5 years
- Pregnant or breastfeeding
- Renal dysfunction (based on individual's report or pharmacy records)
- Immunocompromised state (hematologic malignancy, immunosuppressant drug therapy including corticosteroids for greater than 2 weeks, HIV/AIDS)
- Long-term aspirin therapy in individuals younger than 19 years of age
- Antiviral agent for influenza prescribed currently or within the previous 2 weeks
- Any condition requiring home oxygen therapy
- Known hypersensitivity to all antiviral therapies for influenza and to any common component of the products.
- Receipt of FluMist within past 2 weeks
- Clinically unstable based on the clinical judgment of the pharmacist or any of the following criteria:
  - Acutely altered mental status
  - Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg
  - Pulse >125 beats/min

MEDICATIONS
This protocol authorizes pharmacists to initiate the dispensing of the following antiviral agents. The pharmacist may dispense any dosage form deemed appropriate for the individual.

Oral Oseltamivir dosing:
- **Adults:** 75 mg twice a day x 5 days
- **Children** (current weight determined using pharmacy's scale) x 5 days:
  - **15 kg or less:** 30 mg twice a day
  - **>15 to 23 kg**: 45 mg twice a day
  - **>23 to 40 kg**: 60 mg twice a day
  - **> 40 kg**: 75 mg twice a day

Oral baloxavir dosing:
- **Adults and Children 12 and older:**
  - **40 to less than 80kg:** single dose of 40 mg
  - **80 kg or more:** single dose of 80mg

Inhaled Zanamivir dosing:
- **Adults**: 10mg (two 5mg inhalations) twice a day x 5 days
- **Children (7 years or older):** 10mg (two 5mg inhalations) twice a day x 5 days

https://naspa.us/resource/pharmacist-prescribing-for-strep-and-flu-test-and-treat/. Accessed 11/20/21

CEimpact

28

Does POCT Work?

- Multi-site implementation project, with retrospective data analysis, conducted from July 2014 to May 2016
- A total of 7 pharmacy chains expressed interest in developing POCT services for acute illnesses (e.g., pharyngitis and influenza) plus 2 pharmacy chains from the prospective studies supplied de-identified data
- A 20-hour training program that includes physical assessment, disease state cases, specimen collection, pharmacy law, and risk management was developed/implemented
- Clinical Laboratory Improvement Amendments (CLIA) regulations and waivers were obtained when necessary

Klepser DG, et al., Research in Social and Administrative Pharmacy 2017 http://dx.doi.org/10.1016/j.sapharm.2017.04.012. Accessed 11/15/21

29

Results

Table 2
Summary of patient characteristics.

Age on date of visit (y)	
• Age available for 637/661 patients: Mean (range)	**29.22 years (18-85)**
○ GAS patients (n=539/559)	29.21 years (18-64)
○ Influenza patients (n = 98/102)	30.43 years (19-85)
Gender	
• Gender available (n = 638/661 patients)	**394 Female, 244 Male**
○ GAS patients (n = 540/559)	337 Female, 203 Male
○ Influenza patients (n = 98/98)	57 Female, 41 Male
Presented at pharmacy outside normal clinic hours	
• Pharmacy visit time/day available (n=629/661)	**239/629 (38%)**
○ GAS patients	207/539 (38.4%)
○ Influenza patients	32/90 (35.6%)
Identified a primary care provider	
• Primary care provider status available	123/661(18.6%)
○ GAS patients with a PCP	32/83 (38.6%)
○ Influenza patients with PCP	25/40 (62.5%)

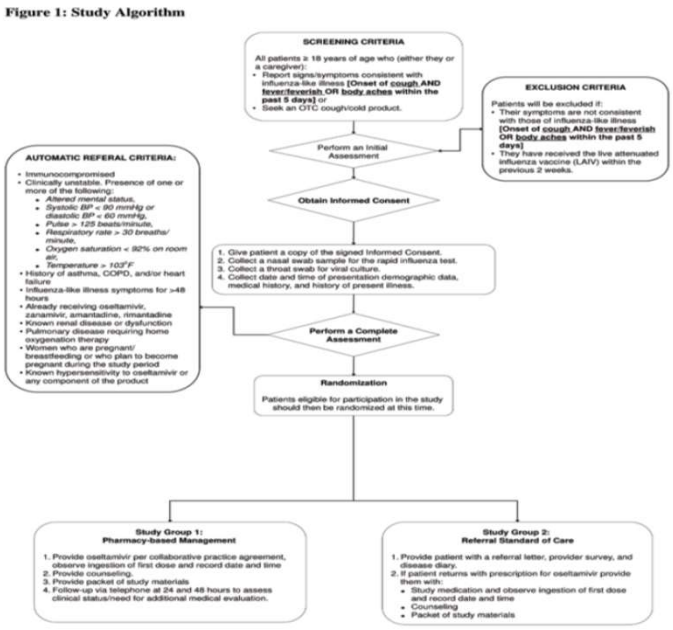
Table 1
Summary of encounters for patients who were tested for influenza or GAS.

	n/N (%)
Patients tested	**661**
• GAS	559/661(84.6%)
• Influenza	102/661 (15.4%)
GAS POC results	**559**
• Results available	540/559 (96.6%)
○ Positive	91/540 (16.9%)
○ Negative	449/540 (83.1%)
GAS Patient treatment at pharmacy	**513/540** (95.0%)
• Positive GAS test with treatment available	90/91 (98.9%)
○ Amoxicillin prescription per CPA	77/90 (85.6%)
○ Azithromycin prescription per CPA	12/90 (13.3%)
○ Contacted PCP to determine treatment	1/90 (1.1%)
• Negative GAS test with treatment available	422/449 (94.0%)
○ Symptomatically/Over-the-counter recommendation	421/422 (99.8%)
○ Referral to Urgent Care	1/422 (0.2%)
Influenza POC results	**102**
• Results available	83/102 (81.4%)
○ Positive	19/83 (22.9%)
○ Negative	64/83 (77.1%)
Influenza Patient treatment at pharmacy	
• Positive influenza test with treatment available	16/19 (84.2%)
○ Oseltamivir prescription per CPA	15/16 (93.8%)
○ Patient refused oseltamivir prescription due to cost, opted for OTC	1/16 (6.3%)
• Negative influenza test with treatment available	25/64 (39.1%)
○ Symptomatically/Over-the-counter recommendation	22/25 (88.0%)
○ Symptomatically and Immunizations recommended	2/25 (8.0%)
○ Referral to Urgent Care	1/25 (4.0%)
Patient was reached for follow-up at 24-48 hours	**90**
• Patient status at follow-up available	
○ Felt better	72/90 (80.0%)
○ Felt the same	13/90 (14.4%)
○ Felt worse	5/90 (5.6%)

CEimpact

30

Same Group: Randomized Control Trial



Klepser ME, et al Illinois Pharmacist 2014; 76: 12-18

CEimpact

31

CEimpact

Results

- 13 pharmacies in four states were identified to serve as study sites
- 22 patients were randomized into Group 1 (n=12) and Group 2 (n=10)
  - No differences in patient demographics
  - BUT only two patients had a positive rapid diagnostic test
  - Eight (66.7%) of the patients in Group 1 and three (30%) in Group 2 received oseltamivir (P>0.05)
- Mean time to the first dose of oseltamivir, among those for whom it was prescribed, was 57.8 minutes (+42.0 minutes) and 385.3 minutes (+421.2 minutes) for patients in Groups 1 and 2, respectively (P=0.04)

https://ncpa.org/point-care-testing-poct. Accessed 10/5/21

32

What About the Nuts and Bolts?

- Recent needs analysis in Wisconsin pharmacies found few currently offer PCOT or test and treat but many are interested in learning how to offer these services
  - As always, execution time, training, and a private area in the pharmacy were listed as major impediments
- Reimbursement?
  - Formal analysis?
    - A 2015 Deloitte study went so far to say that point-of-care testing will surpass immunizations as a revenue driver for retail pharmacies
    - An analysis from GlobalData predicts the market for point-of-care testing to total nearly $3 billion in 2021 - some of that will go to the pharmacy
    - Patients will PAY CASH - $25 to $125 depending on service

https://www.pbahealth.com/point-of-care-testing-a-cash-business-opportunity-for-pharmacy/. Accessed 10/8/21

C.E. Gallimore et al. Journal of the American Pharmacists Association 2021;61: e93-98

33

Bottom Line

- For better or worse, the COVID crisis has shown the general public that a pharmacy can offer/perform lab testing
- Many CLIA waivers exists for such testing
- Most states allow such testing and a growing number allow Test and Treat services
  - Cash payments
  - Significant revenue generator
  - Other public health benefits
- The other side of the issue - how much more can community pharmacies take on without a fundamental change in how they are supported?

34

Gamechanger #3

Semiglutide for weight loss in patients with or without Diabetes

Does it beat the hype or is this "Fen-Fen 2.0"?

35

The Obesity Epidemic

- Obesity is a chronic, relapsing, progressive disease with a multifactorial origin including: genetic, metabolic, behavioral, sociocultural, and environmental factors
- The clinical complications of obesity include cardiovascular diseases, mechanical dysfunction, sleep apnea, and malignancy
- Around 13% to 19.5% of adults globally have obesity, and the prevalence of obesity is predicted to continue to rise. There is a recognition that much of the pathophysiology of obesity involves abnormal satiety and feeding signaling within the brain.
- Lifestyle interventions are the cornerstone of weight management, but alone they are generally associated with moderate weight loss (WL) that is gradually regained.

- Maintaining WL is inherently difficult because of counter-regulatory neuroendocrine pathways that promote weight regain by influencing hunger and satiety, which are a component of appetite, and potentially by decreasing energy expenditure.
- The US Food and Drug Administration and European Medicines Agency have approved AOMs that have been shown to achieve clinically significant WL when used as adjuncts to lifestyle interventions. However, most approved AOMs have moderate efficacy, quantified as a<10% reduction in mean WL over that achieved with lifestyle intervention alone, with significant limitations related to adverse effects, cost, or restrictions on use.
- One potential new AOM is the glucagon-like peptide 1 (GLP-1) analogue semaglutide, which has been developed with these characteristic features in mind.

Blüher, M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15, 288–298

CEimpact

36

Definition of Obesity

- Weight that is higher than what is considered healthy for a given height is described as overweight or obesity.
- Body Mass Index (BMI) is a screening tool for overweight and obesity:
  - BMI 18.5 to <25 falls within the healthy weight range
  - BMI 25.0 to <30 falls within the overweight range
  - BMI 30.0 or higher falls within the obesity range
- Obesity is also frequently subdivided into categories:
  - Class 1: BMI of 30 to < 35
  - Class 2: BMI of 35 to < 40
  - Class 3: BMI of 40 or higher (sometimes categorized as "severe" obesity)

https://www.cdc.gov/obesity/adult/defining.html Accessed 11/1/21

37

GLP-1 Analogue: Mechanism of Action

- Semaglutide is a long-acting GLP-1 analogue that mimics the effects of native GLP-1, which promotes weight loss by reducing energy intake, increasing satiety and satiation, reducing hunger, and enhancing glycemic control.
- Many GLP-1s have been approved for the treatment of T2D, but only liraglutide 3.0 mg daily has been approved for weight management.
- The investigating of semaglutide as a new GLP-1 analogue for the treatment of obesity started because greater weight loss was observed with semaglutide than liraglutide.
- In the phase 2 trial of semaglutide in adults with obesity, a 0.4 mg dose daily was well tolerated, and patients experienced a mean WL at week 52 from baseline of −13.8% compared with −7.8% for liraglutide 3.0 mg and −2.3% for placebo

Kushner RF, et al. Obesity 2020 ;28(6):1050-1061.

38

Aim of the STEP Published Studies (1-4)

- The Semaglutide Treatment Effect in People with obesity (STEP) program aimed to investigate the effect of semaglutide versus placebo on weight loss, safety, and tolerability in adults who are obese or overweight.
- **Study design:** All studies are phase 3, double-blinded, randomized, multicenter, and multinational trials that assess semaglutide (2.4 mg subcutaneously once weekly) versus placebo for WM in adults with obesity or overweight and with and without T2D. Across more than 4 phase 3 trials, ~5,000 participants are being randomly assigned to receive semaglutide 2.4 mg once weekly subcutaneously versus placebo.
- **Primary outcome:** For all trials, the primary end point is change from baseline to end of treatment in body weight. This article covers five of the ongoing phase 3, double-blinded, randomized, multicenter, and multinational trials that assess semaglutide (2.4 mg subcutaneously once weekly) versus placebo for weight management in adults with obesity or overweight and with and without T2D.
- Participants in all treatment groups, including placebo, are receiving the trial product as an adjunct to lifestyle intervention. In all trials except for the weight management with IBT trial (STEP 3), this is defined as a 500-kcal/d deficit relative to the estimated total energy expenditure calculated at randomization together with a recommended 150 min/wk of physical activity.

Kushner RF, et al. Obesity 2020 ;28(6):1050-1061.

39

Trial Objectives

- **Step 1:** To show superiority of semaglutide 2.4 mg versus placebo on WL and to compare safety and tolerability in adults with obesity or overweight, without T2D
- **Step 2:** To show superiority of semaglutide 2.4 mg versus placebo and semaglutide 1.0 mg in WL and to compare safety and tolerability in adults with T2D who are either obese or overweight
- **Step 3:** To maximize the effect of semaglutide 2.4 mg versus placebo in WL in adults with obesity or who are overweight, without T2D
- **Step 4:** To maintain the effect of semaglutide 2.4 mg versus placebo on WL from randomization to EOT and baseline to EOT and to compare safety in adults with obesity or who are overweight who reached the target dose of semaglutide during run-in

40

Outcome Measures

- Primary Endpoint:
  - For all trials, the primary endpoints are percentage change from baseline at randomization to end of treatment (EOT) in body weight and ≥5% weight loss from baseline after EOT (not applicable for the sustained WM trial [STEP 4]).
- Secondary Endpoint:
  - Include the proportion of participants achieving a body weight reduction≥10% or ≥15% from baseline to EOT (not applicable for the sustained WM trial [STEP 4]).
  - change from baseline to EOT (or change from randomization [week 20] to EOT for the sustained WM trial [STEP 4]), in waist circumference (centimeters), systolic blood pressure (millimeters of mercury), and clinical outcome assessments.

41

STEP 1

- Study design: This is a 68-week, randomized, double-blind, placebo-controlled, two-armed, parallel-group, multicenter, multinational clinical trial, with 7 weeks of follow-up without treatment for safety assessments, comparing semaglutide 2.4 mg (subcutaneously, once weekly) with placebo, as an adjunct to lifestyle intervention, in people with obesity or who are overweight. 1,961 adults with obesity or overweight, without T2D, are being randomly assigned in a 2:1 manner to receive semaglutide 2.4 mg or placebo to assess weight loss.
- Results:
  - The findings revealed an average 14.9% reduction in bodyweight from baseline during 68 weeks of treatment with semaglutide 2.4 mg plus a lifestyle intervention, compared with just a 2.4% reduction in the placebo plus lifestyle intervention group (95% confidence interval [CI], −13.4 to −11.5; P<0.001).
  - More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7).
  - Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).
- Conclusion: In participants who are overweight or obese, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight.

JPH Wilding, et al. N Engl J Med 2021; 384:989-1002

CEimpact

42

STEP 2

- **Study design:** From June 4 to Nov 14, 2018, 1595 patients were screened, of whom 1210 were randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or placebo (n=403) and included in the intention-to-treat analysis. This is a 68-week, randomized, double-blind, double-dummy, placebo-controlled, three-armed, multicenter, multinational clinical trial, with 7 weeks of follow-up without treatment for safety assessments, comparing semaglutide 2.4 mg once weekly with placebo, as an adjunct to lifestyle intervention, in people with obesity or overweight and have T2D.
- **Results:**
  - Estimated change in mean bodyweight from baseline to week 68 was −9·6% (SE 0·4) with semaglutide 2·4 mg *vs* −3·4% (0·4) with placebo.
  - Estimated treatment difference for semaglutide 2·4 mg versus placebo was −6·2 percentage points (95% CI −7·3 to −5·2; p<0·0001).
  - At week 68, more patients on semaglutide 2·4 mg than on placebo achieved weight reductions of at least 5% (267 [68·8%] of 388 *vs* 107 [28·5%] of 376; odds ratio 4·88, 95% CI 3·58 to 6·64; p<0·0001).
  - Adverse events were more frequent with semaglutide 2·4 mg (in 353 [87·6%] of 403 patients) and 1·0 mg (329 [81·8%] of 402) than with placebo (309 [76·9%] of 402).
- **Conclusion:** In adults who are overweight or obese with type 2 diabetes, semaglutide 2·4 mg once a week achieved a superior and clinically meaningful decrease in bodyweight compared with placebo.

Davies M, et al. Lancet. 2021 Mar 13;397:971-984

CEimpact

43

STEP 3

- **Study design:** 611 adults with obesity or overweight, without T2D, were randomly assigned in a 2:1 manner to receive semaglutide 2.4 mg or placebo to assess weight loss. Treatment was administered as an adjunct to IBT, in addition to an initial 8-week, low-calorie diet, followed by 60 weeks of a hypocaloric diet and increased physical activity. It comparing semaglutide 2.4 mg (subcutaneously, once weekly) with placebo, as an adjunct to intensive behavioral therapy and low-calorie diet (LCD), in people with obesity or overweight.
- **Results:**
  - Of 611 randomized participants, at week 68, the estimated mean body weight change from baseline was –16.0% for semaglutide vs –5.7% for placebo (difference, −10.3 percentage points [95% CI, −12.0 to −8.6]; *P*<.001).
  - More participants treated with semaglutide vs placebo lost at least 5% of baseline body weight (86.6% vs 47.6%, respectively; *P*<.001).
  - A higher proportion of participants in the semaglutide vs placebo group achieved weight losses of at least 10% or 15% (75.3% vs 27.0% and 55.8% vs 13.2%, respectively; *P*<.001).
  - Gastrointestinal adverse events were more frequent with semaglutide (82.8%) vs placebo (63.2%). Treatment was discontinued owing to these events in 3.4% of semaglutide participants vs 0% of placebo participants.
- **Conclusion:** Among adults who are overweight or obese, once-weekly subcutaneous semaglutide compared with placebo, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss for 68 weeks. Further research is needed to assess the durability of these findings.

Wadden TA et al. JAMA. 2021;325(14):1403-1413.

CEimpact

44

STEP 4

- **Study design:** This is a 68-week, randomized, double-blind, placebo-controlled, two-armed, multicenter, multinational withdrawal clinical trial, with 7 weeks of follow-up without treatment for safety assessments, comparing semaglutide 2.4 mg (subcutaneously, once weekly) with placebo, as an adjunct to lifestyle intervention, in people with obesity or overweight. A total of 902 participants received once-weekly subcutaneous semaglutide during run-in. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), 803 participants (89.0%) who reached the 2.4-mg/wk semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous semaglutide (n=535) or switched to placebo (n=268), plus lifestyle intervention in both groups.
- **Results:**
  - With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs +6.9% with the switch to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; *P*<.001).
  - Waist circumference (−9.7 cm [95% CI, −10.9 to −8.5 cm]), systolic blood pressure (−3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6-3.3]) also improved with continued subcutaneous semaglutide vs placebo (all *P*<.001).
  - Gastrointestinal events were reported in 49.1% of participants who continued subcutaneous semaglutide vs 26.1% with placebo; similar proportions discontinued treatment because of adverse events with continued semaglutide (2.4%) and placebo (2.2%).
- **Conclusion:** Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted

Rubino D, et al. *JAMA.* 2021;325:1414-1425.

CEimpact

45

CEimpact 46

Upcoming Studies:

- **STEP 5:** This long-term weight management trial has 304 participants with obesity or overweight, without T2D, are being randomly assigned in a 1:1 manner to receive semaglutide 2.4 mg or placebo to assess weight loss over a 2-year period- completed but not yet published
- **STEP 6:** This study is like STEP 1, looking at semaglutide versus placebo, but has enrolled people from Japan and Korea and is investigating two possible weekly doses: 1.7 and 2.4 mg- completed but not yet published
- **Step 7:** A trial that looks at overweight or obese patients with or without type 2 diabetes. This trial aims to recruit 375 people – with or without type 2 diabetes – largely across China, but also Hong Kong, the Republic of Korea and Brazil. The participants will receive semaglutide 2.4 mg or placebo for 44 weeks- currently recruiting
- **STEP 8:** This trial looks at overweight or obese patients with type 2 diabetes. Currently enrolled 338 participants and is comparing the weight loss efficacy of semaglutide against the daily injectable GLP-1 receptor agonist liraglutide at its approved dose for obesity, of 3.0 mg. Both medications will also be compared against a matched placebo- active, not yet recruiting

46

Practicalities and Conclusion

- Cost, Cost, Cost
- Nausea - especially if patient has some degree of renal insufficiency
- Gastric slowing
- Boxed warning for history of thyroid cancer

- Bottom Line:
  - 1-2 year data shows safety and efficacy with significant weight loss in the majority of patients
  - Long term safety?

47

Gamechanger #4

Depo Antipsychotics Administered and Monitored in the Community Pharmacy

Critical outreach for patients with mental health disorders

48

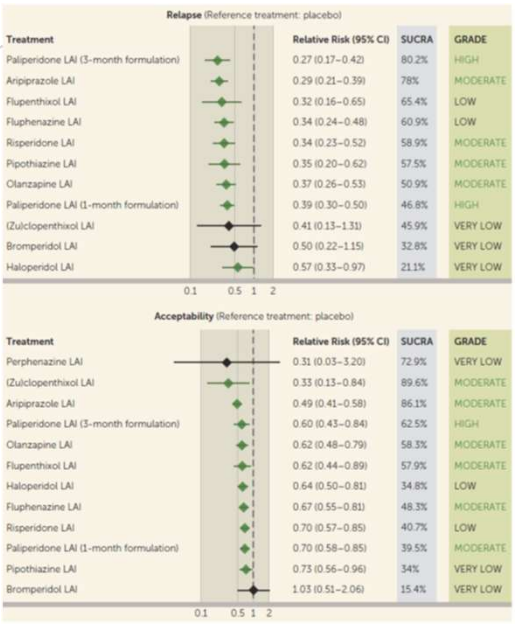
Adherence and the Scope of the Problem

- Schizophrenia is a chronic mental illness that affects an estimated 1% of the population worldwide.
  - Bipolar disorder has an estimated global prevalence of 2.4%
- In 2013, schizophrenia was estimated to create an economic burden of $155.7 billion in the United States.
- Adherence to prescribed medications is important to improve outcomes; however, more than 40% of patients affected by schizophrenia or bipolar disorder are not adherent to their medications.
- One way to improve adherence is by using long-acting injectable antipsychotics (LAIAs).
  - Medication adherence has been shown to be greater with LAIAs compared with oral antipsychotics in patients affected by schizophrenia and in those affected by bipolar disorder
  - LAIAs have been shown to decrease relapse rates, decrease hospitalizations, and improve patient outcomes
  - Overall, treatment with LAIAs was associated with decreased health care costs even though drug costs are higher
- Pharmacists can administer LAIAs in 44 states

American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders Diagnostic and Statistical Manual of Mental Disorders. 5th ed.
Ascher-Svanum H. et al Patient Prefer Adherence. 2008; 2: 67-77
Lin J, et al. J Behav Health Serv Res. 2013; 40: 355-366

DO LAIAs Work Better?

- Meta-analysis of 78 RCTs with 11,505 participants and 12 different LAIAs
- 50% published before 1990
- Generally, all (but especially 2nd gen LAIAs) decreased relapse and were better tolerated



Ostuzzi G, et al. Am J Psychiatry 2021; 178:424–436;

What About NMS and LAIAs?

Table 2. Outcomes of Neuroleptic Malignant Syndrome (NMS)[a,b]

	All Antipsychotics				FGAs				SGAs			
Outcome	LAI n=122 (18.4%)	OAP n=540 (81.6%)	Total n=662 (100%)	*P* Value	FGA-LAI n=112 (26.3%)	FGA-OAP n=314 (73.7%)	Total n=426 (100%)	*P* Value	SGA-LAI n=10 (5.9%)	SGA-OAP n=159 (94.1%)	Total n=169 (100%)	*P* Val
Complete recovery	100 (82.0)	471 (87.2)	571 (86.3)	.2887	91 (81.3)	265 (84.4)	356 (83.6)	.3916	9 (90.0)	146 (91.8)	155 (91.7)	.997
Death	13 (10.7)	36 (6.7)	49 (7.4)	.0861	12 (10.7)	25 (8.0)	37 (8.7)	.1423	1 (10.0)	6 (3.8)	7 (4.1)	.662
Incomplete recovery (sequelae)	9 (7.4)	33 (6.1)	42 (6.3)	.7489	9 (8.0)	24 (7.6)	33 (7.8)	.7724	0 (0)	7 (4.4)	7 (4.1)	.366
Neurologic sequelae[c]	7 (100)	22 (75.9)	29 (80.6)	.8505	7 (100)	17 (77.3)	24 (82.8)	.9619	0 (0)	4 (80)	4 (80)	.580
Cardiovascular sequelae[c]	0 (0)	2 (6.9)	2 (5.6)	**.0001**	0 (0)	2 (9.1)	2 (6.9)	.2909	0 (0)	0 (0)	0 (0)	...
Other sequelae[c]	0 (0)	5 (17.2)	5 (13.9)	.1221	0 (0)	3 (13.6)	3 (10.3)	.3288	0 (0)	1 (20)	1 (20)	.838
Duration of NMS, median (Q_1; Q_3), wk	2.0 (1; 4.3)	1.4 (0.9; 2.3)	1.4 (0.9; 2.6)	.0801	2 (1; 4.3)	1.4 (0.9; 2.4)	1.4 (0.9; 2.9)	**.0357**	1.6 (1; 3.3)	1.3 (0.9; 2.1)	1.3 (0.9; 2.1)	.982
Time onset-death[d], median (Q_1; Q_3), wk	4.6 (0.9; 9)	1.1 (0.7; 3.1)	1.4 (0.8; 4.8)	.3852	4.6 (0.8; 9)	1 (0.7; 4.3)	1 (0.7; 5.1)	.9154	10 (10; 10)	1.6 (0.1; 3.1)	3.1 (0.1; 10)	n/e
Hospital stay, median (Q_1; Q_3), wk	5 (2.1; 8.4)	3.8 (2; 6.2)	4 (2; 6.7)	.8322	6 (2.1; 8.6)	4 (2.3; 9)	4 (2.1; 8.6)	.5169	2.7 (2; 10)	3 (1.3; 4.3)	2.9 (1.3; 4.5)	.872

- Systematic review and analysis of reported cases/cohort studies of NMS
- 662 cases total; no statistically significant difference in outcomes of NMS
- "Clinical presentation, severity, recovery, and mortality did not differ significantly between patients developing NMS during LAI versus OAP treatment"

Guinart D, et al. J Clin Psychiatry 2021;82:2013-27

CEimpact

51

CEimpact

52

How Can Pharmacy Teams Assist?

- Program of Pharmacist administered LAIAs carried out in Albertson's Community Pharmacies.
  - Local mental health clinics refer patients to this service.
  - Pharmacists administer medications by "prescription to administer" from a provider with prescriptive authority.
  - October 2016, approximately 450 pharmacists in the organization were trained to administer LAIAs.
  - Appointments are approximately 30 minutes in duration and are conducted in a private space that is dedicated to patient care.
  - In patients who received LAIAs from pharmacists, a survey was derived from The Patient Satisfaction Questionnaire-18, the Treatment Satisfaction Questionnaire for Medication, and the Client Satisfaction Questionnaires-18 and -8.

Mooney EV, et al, JAPhA 2018;58:24-2

52

Results (n=158) Compared to Usual Services

Table 1
Baseline characteristics

Characteristics	n (%)[a]
State of residence (N = 104)	
Arizona	3 (2.9)
California	24 (23.1)
Colorado	0 (0.0)
Hawaii	1 (1.0)
Idaho	3 (2.9)
Oregon	7 (6.7)
Texas	47 (45.2)
Virginia	3 (2.9)
Washington	16 (15.4)
Age group (N = 104)	
<40 years old	65 (62.5)
≥40 years old	39 (37.5)
Sex[b] (n = 102)	
Female	36 (35.3)
Male	66 (64.7)
Number of years with current condition[c] (n = 100)	
<1	8 (8.0)
1–5	49 (49.0)
6–10	15 (15.0)
>10	28 (28.0)
Number of months using this service[d] (n = 101)	
<1	5 (5.0)
1–6	25 (24.8)
7–12	24 (23.8)
13–18	14 (13.9)
19–24	12 (11.9)
>24	21 (20.8)

Table 2
Patient satisfaction and service comparison

Statement	Positive responses (n, %)	Neutral responses (n, %)	Negative responses (n, %)
Patient satisfaction (N = 104)			
Level of privacy	102 (98.1)	2 (1.9)	0 (0.0)
Ease of scheduling appointment	89 (85.6)	7 (6.7)	8 (7.7)
Comfort with service provided by pharmacy	102 (98.1)	1 (0.9)	1 (0.9)
Convenience of location	67 (64.4)	20 (19.2)	17 (16.3)
Trust in pharmacist	100 (96.1)	3 (2.9)	1 (0.9)
Clear pharmacist communication	98 (94.2)	1 (0.9)	5 (4.8)
Pharmacist listening skills	101 (97.1)	3 (2.9)	0 (0.0)
Confidence in pharmacist's ability to administer medication	102 (98.1)	2 (1.9)	0 (0.0)
Pharmacist knowledge about service provided	101 (97.1)	3 (2.9)	0 (0.0)
Unrushed appointment	100 (96.1)	2 (1.9)	2 (1.9)
Likelihood of recommending service to others	97 (93.3)	5 (4.8)	2 (1.9)
Service comparison (n = 57)			
I trusted the RPh as much or more	53 (93.0)	4 (7.0)	0 (0.0)
The RPh communicated the process as clearly	51 (89.5)	2 (3.5)	4 (7.0)
The RPh was as knowledgeable or more	44 (77.2)	11 (19.3)	2 (3.5)
The RPh listened as carefully	53 (93.0)	4 (7.0)	0 (0.0)
This service was more convenient	46 (82.1)	5 (8.9)	5 (8.9)

Abbreviation used: RPh, registered pharmacist.
[a] One patient opted not to answer (n = 56).

CEimpact

53

CEimpact 54

Bottom Line

- 2nd generation LAIAs are safe and effective and may have significant advantages over oral medications of the same class
- Community pharmacists can administer these agents in many states
  - Increased access and perhaps adherence
  - Monitoring for ADRs
- Reimbursement?
- I know, I know - one more thing for the community pharmacy team to manage …

54

QUESTIONS?

Geoffrey C. Wall, PharmD, FCCP, BCPS

Geoff.wall@drake.edu

Twitter: @nuwavepharm

Gamechangers Podcast

55