

## Respiratory Medication Update

Mark Malesker, Pharm.D., FCCP, FCCP, FCCM, FASHP, BCPS  
Professor of Pharmacy Practice and Medicine  
Creighton University

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## Objectives

- Recognize newly approved respiratory products and significant new dosage forms
- Discuss the indications and side effect potential for each agent
- Identify updated evidence based respiratory treatment guidelines



## Faculty Disclosure

Mark A. Malesker, Pharm.D.

Dr. Malesker has listed no financial interest/arrangement that would be considered a conflict of interest



## Audience Question #1

- How many new novel medications were FDA approved in 2018 ?
- A. 22
- B. 33
- C. 59
- D. 67

## Audience Question #2

- What is the dose for Glycopyrrolate (Lonhala Magnair) ?
- A. 25 mcg one daily
- B. 25 mcg twice daily
- C. 25 mcg three times daily
- D. 25 mcg every 4 hours PRN

## Audience Question #3

- What is the indication for cannabidiol (Epidiolex)?
- A. Seizures
- B. Pain
- C. End stage COPD
- D. Obstructive sleep apnea

## 2018 Drug Approvals

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- The FDA approved 59 novel new drugs and biologics,
  - Average of 33 for 2009-2017
- First in class (19/59) 32%
  - Drugs with a new and unique mechanism for treating a medical condition
- Orphan drugs (34/59) 58%
  - Drugs approved for small populations of patients with rare diseases (200,000 or fewer Americans)
  - 6800 rare diseases identified affecting 30 million people
- Breakthrough (14/59) 24%
  - A drug with preliminary clinical evidence demonstrating that it may result in substantial improvement on at least one clinically significant endpoint over other available therapies

www.fda.gov/drugs

## 2018 Drug Approvals

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- Fast track (24/59) 41%
  - Drugs that can treat unmet medical needs
- Priority review (43/59) 73%
  - A drug is given priority review if there is a potential to provide a significant advance in existing medical care and set a target to review within six months
- Accelerated approval (4/59) 7%
  - Early approval based on markers that predict a reasonable benefit, with more testing to confirm clinical benefit after approval

www.fda.gov/drugs

## 2017 Drug Approvals

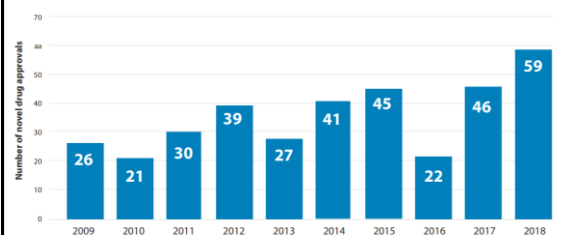
9

- First cycle (56/59) 45%
  - Drugs that were approved without additional information that could delay approval and lead to another cycle of review
- First approved in U.S. (42/59) 71%
  - Drugs that were approved in the United States before approved in other country

www.fda.gov/drugs

## Novel Drug Approvals 2009-2018

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## Correct Inhaler Technique

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- Center for Disease Control and Prevention (CDC)
  - [https://www.cdc.gov/asthma/inhaler\\_video/](https://www.cdc.gov/asthma/inhaler_video/)
- Allergy and Asthma Network
  - [https://www.youtube.com/playlist?list=PLC39F35D440D0F155&feature=view\\_all](https://www.youtube.com/playlist?list=PLC39F35D440D0F155&feature=view_all)
- Institute for Safe Medication Practices (ISMP)
  - <https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=1143>
- <http://use-inhalers.com/>
- Product specific websites

## Respiratory Pharmacology Inhalation Therapy

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- Beta<sub>2</sub>-agonists
  - Short-acting beta-agonists (SABA)
  - Long-acting beta-agonists (LABA)
- Anticholinergics
  - Short-acting antimuscarinic agent (SAMA)
  - Long-acting antimuscarinic agent (LAMA)
- Combined SABA/SAMA
- Combined LABA/LAMA
- Inhaled corticosteroids (ICS)
- Combined LABA/ICS
- Combined LABA/LAMA/ICS

## Short-Acting Beta-Agonists (SABA)

13

Agent	Formulation	Dose
Albuterol generic	Nebulizer	1.25-5 mg q4-6h PRN
Albuterol HFA MDI (ProAir, Proventil, Ventolin)	MDI	2 inhalations q4-6h PRN
Albuterol (ProAir RespiClick)	DPI	1-2 inhalations q4-6h PRN
Albuterol (ProAir Digihaler)	DPI	1-2 inhalations q4-6h PRN
Levalbuterol generic	Nebulizer	0.31-1.25 mg tid q6-8h
Levalbuterol (Xopenex HFA)	MDI	2 inhalations q4-6h PRN

MDI = metered dose inhaler, DPI = dry powder inhaler

## Albuterol (ProAir Digihaler)

14

- Shake before use?
  - No
- Priming
  - No
- Cleaning
  - Wipe mouthpiece as needed
- Dose counter
  - Yes
- Beyond use date
  - 13 months after removal from foil pouch



Contains built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App

<https://www.proairdigihaler.com/>

## Generic Albuterol Inhaler

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- On January 17, 2019, Teva launched an authorized generic version of ProAir HFA (albuterol) inhalation aerosol
- Teva also markets branded ProAir

## Epinephrine (Primatene Mist)

16

- 2011
- 2018



## Epinephrine (Primatene Mist HFA)

17

- Returns to market in 2018 after 7 year absence
- OTC for intermittent asthma ( $\geq 12$  years)
- Racemic epinephrine is not recommended treatment
  - Each dose delivers 0.125 mg of epinephrine (160 doses)
  - Dosage is 1-2 inhalations every 4 hours, max 8 puffs/24<sup>o</sup>
- AAN, ACAAI, ACCP, ALA, ATS all oppose approval
- Activate before use, clean every day
- Shake and spray once into air before each use
- Seek medical attention if no relief in 20 minutes, symptoms get worse, use more than 8 puffs in 24 hours or more than 2 attacks per week
- Cost \$29.99

<https://www.primatene.com>

## Long-Acting Beta Agonists (LABA)

18

Agent	Formulation	Dose
Salmeterol (Serevent Diskus)	DPI	1 inhalation bid
Formoterol (Perforomist)	Nebulizer	20 mcg bid
Arformoterol (Brovana)	Nebulizer	15 mcg bid
Indacaterol (Arcapta)	DPI	75 mcg capsule once daily
Olodaterol (Striverdi Respimat)	ISI	2 inhalations daily

DPI = dry powder inhaler, ISI = inhalation spray inhaler

## Short-Acting Anticholinergic (SAMA)

19

Agent	Formulation	Dose
Ipratropium generic	Nebulizer	500 mcg qid PRN
Ipratropium (Atrovent HFA)	MDI	2 inhalations qid PRN

## Long-Acting Anticholinergic (LAMA)

20

Agent	Formulation	Dose
Tiotropium (Spiriva HandiHaler)	DPI	18 mcg capsule once daily
Tiotropium (Spiriva Respimat)	ISI 2.5 mcg	2 inhalations (5 mcg) once daily for COPD
Tiotropium (Spiriva Respimat)	ISI 1.25 mcg	2 inhalations (2.5 mcg) once daily for Asthma
Acclidinium (Tudorza Pressair)	DPI	400 mcg twice daily
Umeclidinium (Incruse Ellipta)	DPI	1 inhalation daily
Glycopyrrolate (Seebri Neohaler)	DPI	15.6 mcg capsule twice daily

DPI = dry powder inhaler, ISI = inhalation spray inhaler

## Long-Acting Anticholinergic (LAMA)

21

Agent	Formulation	Dose
Glycopyrrolate (Lonhala Magnair)	Nebulizer	<ul style="list-style-type: none"> <li>25 mcg/1 ml vial twice daily</li> <li>Used in portable, handheld, electronic nebulizer</li> </ul>
Revefenacin (Yupelri)	Nebulizer	<ul style="list-style-type: none"> <li>175 mcg/3ml once daily</li> <li>Used in standard jet nebulizer</li> </ul>

## Glycopyrrolate (Lonhala Magnair)

22

- First nebulized LAMA for long term maintenance of COPD
- Dose is one vial (25 mcg) twice daily
- Magnair eFlow system, developed by Pari Pharma
  - Portable, virtually silent, delivers drug in 2-3 minutes
- Approval based upon GOLDEN trials which compared glycopyrrolate to placebo in moderate to severe COPD
- Improved lung function and health status regardless of lung function or age (pooled analysis)
- Side effects ( $\geq 2\%$ ) were dyspnea and UTI
- Drug interactions with other anticholinergics

<https://www.lonhalamagnair.com>

## Glycopyrrolate (Lonhala Magnair)

23



## Revefenacin (Yupelri)

24

- LAMA given once daily 175 mcg (3 ml) over 8-10 minutes by standard jet nebulizer for maintenance treatment of COPD
- Can cause dry mouth, urinary retention
- Avoid concurrent use of rifampin, cyclosporine, anticholinergics
- Avoid with hepatic impairment



<https://dailymed.nlm.nih.gov/dailymed/foia/foiaDrugX.cfm?setid=6dfe8047-90436a-9b16-750d3c1ee0a&type=display>

## SABA/SAMA Combination

25

Agent	Formulation	Dose
Albuterol/ipratropium (Combivent Respimat)	ISI	1 inhalations q 6 hrs
Albuterol/ipratropium (DuoNeb)	Nebulizer	2.5 mg/0.5 mg qid PRN

## LAMA/LABA Combination

26

Agent	Formulation	Delivery Device	Dosage
Umeclidinium/vilanterol (Anoro Ellipta)	62.5 mcg/25 mcg	DPI	1 inhalation daily
Tiotropium/olodaterol (Stiolto Respimat)	2.5 mcg/2.5 mcg	ISI	2 inhalations once daily
Glycopyrrolate/indacaterol (Utibron Neohaler)	15.6 mcg/27.5 mcg capsule	DPI	1 capsule daily
Glycopyrrolate/formoterol (Bevespi Aerosphere)	9 mcg/4.8 mcg	MDI	2 inhalations twice daily

DPI = dry powder inhaler, ISI = inhalation spray inhaler

## Inhaled Corticosteroids (ICS) (1)

27

Agent	Delivery	Dose
Beclomethasone (QVAR HFA) 40, 80 mcg/inhalation	MDI	40-320 mcg bid
Beclomethasone (QVAR Redihaler)	MDI	40-320 mcg bid
Budesonide (Pulmicort Respules)	Nebulizer	250-500 mcg 1x/d or bid or 1 mg 1x/d
Budesonide (Pulmicort Flexhaler) 90, 180 mcg/inhalation	DPI	180-720 mcg bid
Ciclesonide (Alvesco) 80, 160 mcg/inhalation	MDI	80-320 mcg bid
Flunisolide (Aerospan HFA) 80 mcg/inhalation	MDI	160-320 mcg bid

## Beclomethasone Dipropionate (QVAR)

28

- Shake well before use?
  - No
- Priming
  - Before the first use, or if not used for more than 10 days: 2 sprays
- Cleaning
  - At least weekly
- Dose counter: Yes
- Beyond use date
  - Exp date on package



Product discontinued in Aug 2017, available till March 2018

[www.qvar.com](http://www.qvar.com)

## Beclomethasone Dipropionate HFA (QVAR RediHaler)

29

- Shake well before use?
  - No
- Priming
  - No
- Cleaning
  - At least weekly
- Dose counter: Yes
- Beyond use date
  - Exp date on package



- FDA approved in August 2017
- Only breath activated ICS

<https://www.qvar.com/>

## Inhaled Corticosteroids (ICS) (2)

30

Agent	Delivery	Dose
Fluticasone propionate (Flovent Diskus) 50, 100, 250 mcg/blister	DPI	100-1000 mcg bid
Fluticasone propionate (Flovent HFA) 44, 110, 220 mcg/inhalation	MDI	88-880 mcg bid
Fluticasone propionate (ArmonAir RespiClick) 55, 113, 232 mcg/inhalation	DPI	55-232 mcg bid

## Inhaled Corticosteroids (ICS) (3)

Agent	Delivery	Dose
Fluticasone furoate (Arnuity Ellipta) 100, 200 mcg/inhalation	DPI	100-200 mcg once daily
Mometasone (Asmanex Twisthaler) 110, 220 mcg/inhalation	DPI	220-880 mcg once/day in evening or 220 mcg bid
Mometasone (Asmanex HFA) 100, 200 mcg/inhalation	MDI	200-400 mcg twice daily


## ICS/LABA Combination

Agent	Formulation	Delivery Device	Dosage
Fluticasone propionate/salmeterol (Advair Diskus)	100, 250, 500/50 mcg	DPI	1 inhalation bid
Fluticasone propionate/salmeterol (Advair HFA)	45, 115, 230 mcg/21 mcg	MDI	2 inhalations bid
Fluticasone/salmeterol (AirDuo RespiClick)	55, 113, 232 mcg/14 mcg	DPI	1 inhalation bid
Fluticasone furoate/vilanterol (Breo Ellipta)	100 mcg/25 mcg	DPI	1 inhalation daily
Budesonide/formoterol (Symbicort)	80, 160 mcg/4.5 mcg	MDI	2 inhalations bid
Mometasone/formoterol (Dulera)	100, 200 mcg/5 mcg	MDI	2 inhalations bid

## Fluticasone/Salmeterol (Wixela Inhub)

Agent	Formulation	Delivery Device	Dosage
Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)	100 mcg, 62.5 mcg, 25 mcg	DPI	1 inhalation daily


- ❑ Mylan generic Advair Diskus approved Jan 30, 2019
- ❑ GSK generic Advair launched Feb 8, 2019
- ❑ 100/250/500 mcg/50 mcg
- ❑ WAC 70% less than Advair and 67% less than GSK generic



<https://www.drugstorenews.com/news/mylan-gets-fdas-approval-for-first-generic-advair-diskus/>

## ICS/LAMA/LABA Combination

- ❑ Shake before use?
  - ❑ No
- ❑ Priming
  - ❑ No
- ❑ Cleaning
  - ❑ If desired
- ❑ Dose counter
  - ❑ Yes
- ❑ Beyond use date
  - ❑ 6 weeks after removal from foil pouch or when counter reads 0



FDA approved 9-18-17

<https://www.trelegy.com>

## Amikacin Liposome Inhalation Suspension (Arikayce)

- ❑ Aminoglycoside indicated in adults who have limited or no alternative treatments options for *Mycobacterium avium* complex (MAC) as part of a combination drug regimen
- ❑ Only studied in refractory MAC
- ❑ Dose is 590 mg/8.4 ml once daily
  - ❑ Use with Lamira Nebulizer System over 14-20 minutes
- ❑ Use pretreatment with inhaled bronchodilator
- ❑ Boxed warning for increased respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases

<https://www.arikayce.com/pdf/full-prescribing-information.pdf>

## Amikacin (Arikayce)



## Levodopa (Inbrija)

- Inhalation powder for Parkinson's disease
- Inhale contents of two capsules (84 mg) as need for OFF symptoms up to 5 times daily
- Use only with Inbrija breath-actuated inhaler
- Whirl sound with inhalation
- Side effects ≥5%: cough, nausea, URI, sputum discolored



<https://www.inbrija.com/prescribing-information.pdf>

## Baloxavir Marboxil (Xofluza)

- Endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours
- Single dose: (80 kg and above) 80 mg
- Avoid co-administration with dairy products, cations

[https://www.gene.com/download/pdf/xofluza\\_prescribing.pdf](https://www.gene.com/download/pdf/xofluza_prescribing.pdf)

## Tezacaftor/Ivacaftor (Symdeko)

- Fixed dose combination for oral treatment of cystic fibrosis in patients ≥ 12 years old who are homozygous for the F508del (also called Phe508del or ΔF508) mutation or have at least one mutation in the fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to the combination
- About 50% of CF patients in USA are homozygous for the F508del mutation
- Combination improves pulmonary function
- Expensive

[https://pi.vrtx.com/files/uspi\\_tezacaftor\\_ivacaftor.pdf](https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf)

## Monoclonal Antibodies for Asthma

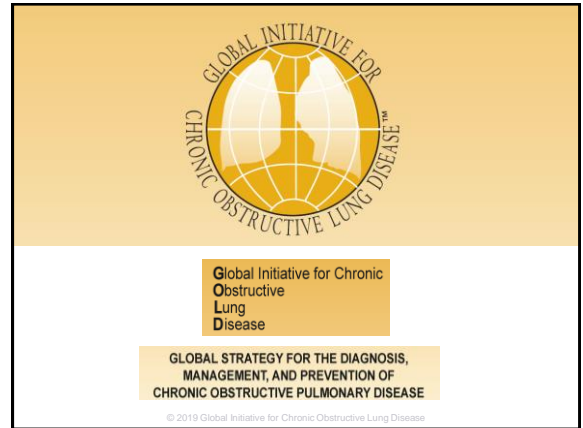
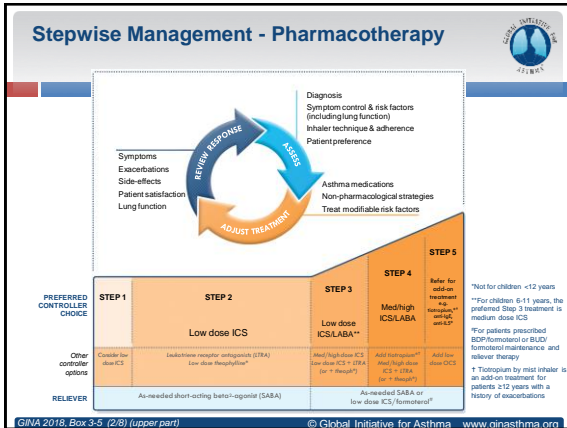
	Benralizumab (Fasenra)	Mepolizumab (Nucala)	Reslizumab (Cinqair)	Dupilumab (Dupixent)
Mechanism of action	IL-5 receptor antagonist	IL-5 antagonist	IL-5 antagonist	IL-4 receptor alpha subunit antagonist
Formulation	Prefilled syringe	Single dose vials	Single use vials	Prefilled syringe
Dosage	30 mg SC q4 weeks x 3, then q8 weeks	100 mg SC q4 weeks	3 mg/kg IV q4 weeks	400 mg SC then 200 mg q2 weeks, or 600 mg SC then 300 mg q2 weeks
FDA approved Age	≥ 12 years	≥ 12 years	≥ 18 years	≥ 12 years

[https://www.regeneron.com/sites/default/files/Dupixent\\_FPI.pdf](https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf)

## Global Initiative for Asthma (GINA) Guidelines

- What factors may predict good response to anti-IL5/5R?
  - Higher blood eosinophils (≥300/μl)
  - More exacerbations in previous year
  - Adult-onset of asthma
  - Nasal polyposis

<https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf>



## GOLD Guidelines Pharmacologic Therapy

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- Pharmacological therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status
- To date, there is no conclusive clinical trial evidence that any existing medications for COPD modify the long-term decline in lung function
- The choice within each class depends on the availability and cost of medication and favourable clinical response balanced against side effects
- Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations can differ between patients

## Smoking Cessation

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- Smoking cessation has the greatest capacity to influence the natural history of COPD.
- If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved.

**BRIEF STRATEGIES TO HELP THE PATIENT WILLING TO QUIT**

- ASK:** Systematically identify all tobacco users at every visit. Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.
- ADVISE:** Strongly urge all tobacco users to quit. In a clear, strong, and personalized manner, urge every tobacco user to quit.
- ASSESS:** Determine willingness and rationale of patient's desire to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
- ASSIST:** Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide extra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
- ARRANGE:** Schedule follow-up contact. Schedule follow-up contact, either in person or via telephone.

TABLE 3.1 © 2019 Global Initiative for Chronic Obstructive Lung Disease

## Common Canister Policy

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- Efforts intended to curb rising costs and waste associated with MDI use, have resulted in a variety of protocols generically referred to as CCPs
- Allows a single MDI canister to be shared among patient in a designated care area (hospital ward) with each individual having his/her own one-way valve holding chamber or spacer
- The safety of CCP hinges on proper cleaning of the MDI between users
- Before initiating CCP, communication should occur among risk managers, the P&T committee, pulmonologists, respiratory therapists, the medical executive committee, infection control personnel, and the professional liability insurance provide

<https://www.mdedge.com/chestphysician/article/113875/critical-care/common-canister-policy-devil-details/page/0/1>

## Audience Question #4

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- A generic equivalent exists for what ICS/LABA combination product ?
  - A. Budesonide/formoterol (Symbicort)
  - B. Mometasone/formoterol (Dulera)
  - C. Fluticasone propionate/salmeterol (Advair)
  - D. Fluticasone furoate/vilanterol (Breo Ellipta)



## Audience Question #5

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- Where is revefenacin (Yupelri) best utilized ?
  
- A. Acute treatment of asthma
- B. Acute treatment of COPD
- C. Chronic treatment of asthma
- D. Chronic treatment of COPD

## Audience Question #6

50

- What is the dose for amikacin (Arikayce) for the treatment of MAC?
  
- A. Once daily
- B. Twice daily
- C. Three times daily
- D. Four times daily

## The End

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