Pulmonary and Critical Care Medication Update 2022

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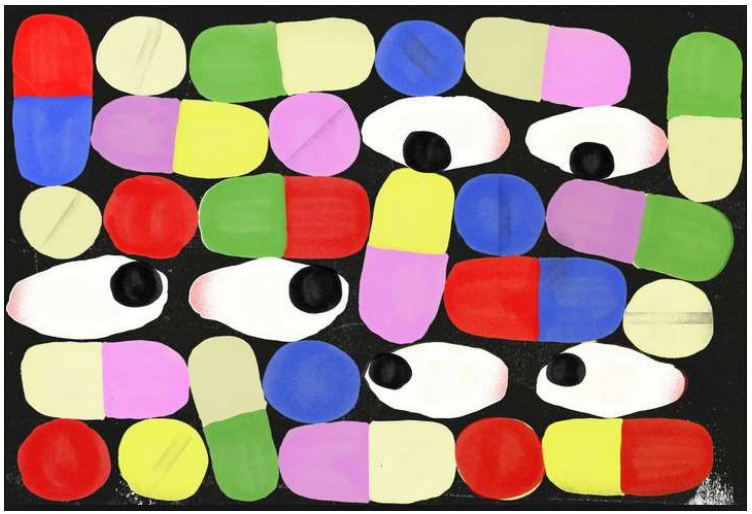
Faculty Disclosure

Mark A. Malesker, Pharm.D.

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



Objectives

- Recognize newly approved pharmaceutical products and significant new dosage forms
- Discuss the indications, contraindications, dosage, drug interaction potential, and side effect potential for each agent
- Identify the place in therapy for each agent

Audience Question #1

- How many new novel medications were FDA approved in 2021 ?

- A. 27
- B. 39
- C. 50
- D. 59

Audience Question #2

- What is the indication for difelikefalin (Korsuva) ?

- A. ANCA-associated vasculitis
- B. Non-small cell lung cancer
- C. Pompe disease
- D. Pruritis with chronic kidney disease

Audience Question #3

- What is the mechanism of action for Tezepelumab (Tezspire)?

- A. Anti-IgE monoclonal antibody
- B. Interleukin-4 and Interleukin-13 receptor antagonist
- C. Interleukin-5 receptor antagonist
- D. Thymic stromal lymphopoietin (TSLP) blocker

2021 Drug Approvals

- The FDA approved 50 novel new drugs and biologics
  - Average of 43 for 2012-2021
- First in class (27/50) 54%
  - Drugs with a new and unique mechanism for treating a medical condition
- Orphan drugs (26/50) 52%
  - Drugs approved for small populations of patients with rare diseases (200,000 or fewer Americans)
  - 6800 rare diseases identified affecting 30 million people
- Breakthrough (14/50) 28%
  - Drugs for serious or life-threatening diseases for which there is unmet need and for which there is preliminary clinical evidence demonstrating that the drug may result in substantial improvement on a clinically significant endpoint

2021 Drug Approvals

- **Fast track (18/50) 36%**
  - **Drugs that have potential to address unmet medical needs, speeds new development and review**
- **Priority review (34/50) 68%**
  - **A drug is given priority review if there is a potential to provide a significant advance in existing medical care, reviewed within eight months (standard 12 months)**
- **Accelerated approval (14/50) 28%**
  - **Early approval based on markers that predict a reasonable benefit, with more testing to confirm clinical benefit after approval**

2021 Drug Approvals

- First cycle (43/50) 86%
  - Drugs that were approved without additional information that could delay approval and lead to another cycle of review
- First approved in U.S. (38/50) 76%
  - Drugs that were approved in the United States before approved in another country

Novel Drug Approvals 2012-2021

www.fda.gov

2021 Drug Approvals (1)

Brand	Generic	Description
Adbry	Tralokinumab-ldrm	Atopic dermatitis
Aduhelm	Aducanumab-avwa	Alzheimer's disease
Amondys 45	Casimersen	Duchenne muscular dystrophy
Azstarys	Serdexmethylphenidate/ dexmethylphenidate	ADHD
Besremi	Ropeginterferon alfa-2b-njft	Polycythemia vera
Brexafemme	Ibrexafungerp	Vulvogaginal candidiasis

2021 Drug Approvals (2)

Brand	Generic	Description
Bylvay	Odevixibat	Pruritis in cholestasis
Cabenuva	Cabotegravir/ rilpivirine	HIV
Cosela	Trilaciclib	Small cell lung cancer
Cytalux	Pafolacianine	Ovarian cancer imaging
Empaveli	Pegcetacoplan	Nocturnal hemoglobinuria
Evkeeza	Evinacumab-dgnb	Familial hypercholesterolemia
Exkivity	Mobocertinib	Non-small cell lung cancer

2021 Drug Approvals (3)

Brand	Generic	Description
	Fexinidazole	African trypanosomiasis
Fotivda	Tivozanib	Renal cell carcinoma
Jemperli	Dostarlimab-gxly	Endometrial cancer
Kerendia	Finerenone	Reduce risk in chronic kidney disease associated with DM II
Korsuva	Difelikefalin	Pruritis with chronic kidney disease
Leqvio	Inclisiran	Familial hypercholesterolemia
Livmarli	Maralixibat	Cholestatic pruritis in Alagille syndrome
Livtencity	Maribavir	Cytomegalovirus infection

2021 Drug Approvals (4)

Brand	Generic	Description
Lumakras	Sotorasib	Non-small cell lung cancer
Lupkynis	Voclosporin	Lupus nephritis
Lybalvi	Olanzapine and samidorphan	Schizophrenia and bipolar 1 disorder
Nextellis	Drospereone/ estetrol	Oral contraceptive
Nexviazyme	Avalglucosidase alfa-ngpt	Late onset Pompe disease
Nulibry	Fosdenopterin	Molybdenum cofactor deficiency Type A

2021 Drug Approvals (5)

Brand	Generic	Description
Pepaxto	Melphalan flufenamide	Refractory multiple myeloma
Ponvory	Ponesimod	Multiple sclerosis
Pylarify	Piflufolastat F18	Radioactive diagnostic agent for PET scans of prostrate cancer
Qelbree	Viloxazine	Selective norepinephrine reuptake inhibitor for ADHD
Qulipta	Atogepant	Episodic migraines
Rezurock	Belumosudil	Chronic graft-vs-host disease
Rybrevant	Amivantamab-vmjw	Small Cell lung cancer

www.fda.gov

2021 Drug Approvals (6)

Brand	Generic	Description
Rylaze	Asparaginase erwinia chrysanthemi	Acute lymphoblastic leukemia and lymphoma in pts allergic to *E. coli* derived asparaginase
Saphnelo	Anifrolumab-fnia	Lupus erythematosus
Scemblix	Asciminib	Chronic myeloid leukemia
Skytrofa	lonapegsomatropin-tcgd	Short stature
Tavneos	Avacopan	ANCA associated vasculitis
Tepmetko	Tepotinib	Non-small cell lung cancer
Tezspire	Tezepelumab-ekko	Severe asthma
Tivdak	Tisotumab vedotin-tftv	Cervical cancer

www.fda.gov

2021 Drug Approvals (7)

Brand	Generic	Description
Truseltiq	Infigratinib	Cholangiocarcinoma
Ukoniq	Umbralisib	Lymphoma
Verquvo	Vericiguat	Chronic heart failure
Voxzogo	Vosoritide	Achondroplasia
Vyvgart	Efgartiimod alfa-fcab	Myasthenia gravis
Welireg	Belzutifan	von Hippel-Lindau disease
Zegalogue	Dasiglucagon	Severe hypoglycemia
Zynlonta	loncastuximab tesirine-lpyl	B-cell lymphoma

2021 New Indications (1)

Brand	Generic	Description
Actemra	Tocilizumab	Systemic sclerosis-associated ILD
Apretude	Cabotegravir	PrEP for HIV-1
Dartisla	Glycopyrrolate	ODT for peptic ulcer
Entadfi	Finasteride/ tadalafil	BPH
Farxiga	Dapagliflozin	Heart failure
Invega Hafyera	Paliperidone	Schizophrenia
Kloxxado	Naloxone	Opioid overdose

2021 New Indications (2)

Brand	Generic	Description
Prograf	Tacrolimus	Organ rejection in lung transplant
Roszet	Rosuvastatin/ ezetimibe	Reduce CV risk
Seglentis	Celecoxib/ tramadol	Acute pain
Tarpeyo	Budesonide	PO for immunoglobin A nephropathy
Tyrvaya	Varenicline	Nasal spray for dry eyes
Uptravi	Selexipag	Injection formulation
Wegovy	Semaglutide	Weight loss

www.fda.gov

2021 New Indications (3)

Brand	Generic	Description
Zimhi	Naloxone	Prefilled syringe for opioid overdose
Zynrelef	Bupivacaine/ meloxicam	Postsurgical analgesia

2022 Drug Approvals

Brand	Generic	Description
Amvuttra	Vutrisiran	Hereditary transthyretin-mediated amyloidosis
Camzyos	Mabacamten	Obstructive hypertrophic cardiomyopathy
Mounjaro	Tirzepatide	GLP-1 for type 2 diabetes
Pyrukynd	Mitapivat	Hemolytic anemia
Quviviq	Daridorexant	Insomnia
Tyvaso	Trepostinil	DPI for PAH, PH-ILD
Ztalmy	Ganaxolone	Cyclin-dependent kinase-like 5 deficiency disorder
Terlivaz	Terlipressin	Hepatorenal syndrome

2022 New Formulations

Brand	Generic	Description
Adlarity	Donepezil	Transdermal patch for Alzheimer's dementia
Aspruzyo Sprinkle	Ranolazine	ER formulation for angina
Dapzura RT	Daptomycin	New formulation
Igalmi	Dexmedetomidine	SL film formulation
Tadliq	Tadalafil	Oral suspension
Xelstrym	Dextroamphetamine	Topical patch for ADHD
Aponvie	Aprepitant	PONV

Dexmedetomidine (Igalmi)

- α-2 adrenergic receptor agonist indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults
- The safety and effectiveness has not been established beyond 24 hours from the first dose
- Administer sublingually or buccally - do not chew or swallow
- Adverse reactions (incidence ≥5% and at least twice the rate of placebo) are somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension
- Warning: hypotension, orthostatic hypotension, and bradycardia
- Drugs that prolong QT interval: avoid use

https://www.igalmihcp.com/igalmi-pi.pdf

Dexmedetomidine (Igalmi) Dosing

Patient Population	Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Adults	Mild or Moderate	120 mcg	60 mcg	240 mcg
	Severe	180 mcg	90 mcg	360 mcg
Patients with Mild or Moderate Hepatic Impairment†	Mild or Moderate	90 mcg	60 mcg	210 mcg
	Severe	120 mcg	60 mcg	240 mcg
Patients with Severe Hepatic Impairment†	Mild or Moderate	60 mcg	60 mcg	180 mcg
	Severe	90 mcg	60 mcg	210 mcg
Geriatric Patients (≥ 65 years old)	Mild, Moderate, or Severe	120 mcg	60 mcg	240 mcg

https://www.igalmihcp.com/igalmi-pi.pdf

Daridorexant (Quviviq)

- Treatment of sleep-onset insomnia and/or sleep- maintenance insomnia in adults
- Suppresses the wake drive by competitively inhibiting orexin A and B from binding to OX1R and OX2R
- Dosage is 25 or 50 mg once nightly $\leq$ 30 minutes before bedtime and $\geq$ 7 hours before planned awakening
- Side effects ($\geq$5%): headache, somnolence, fatigue
  - Excessive daytime sleepiness, sleep paralysis, hallucinations reported
- Use with strong CYP3A4 inhibitors or strong or moderate CYP3A4 inducers is not recommended; maximum dose with moderate CYP3A4 inhibitors in 25 mg
- Schedule IV controlled substance
- Modestly more effective than placebo, generally well tolerated, no active-comparator trials

https://www.quviviq.com/

Treprostinol (Tyvaso DPI)

- Prostacyclin mimetic indicated for (PAH; WHO Group 1), (PH-ILD; WHO Group 3)
- Administer using a single inhalation per cartridge
- Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours
- Initial dosage: one 16 mcg cartridge per treatment session
  - Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals, if tolerated
- Titrate to target maintenance doses of 48 mcg to 64 mcg per treatment session, 4 times daily

https://www.tyvasohcp.com/ph-ild/

Selexipag (Uptravi)

- New dosage form (1800 mcg lyophilized powder in a single-dose vial)
- Use injection in patients who are temporarily unable to take oral therapy
- Administer injection twice daily by intravenous infusion at a dose that corresponds to the patient's current dose of selexipag tablets
- Given as an 80-minute intravenous infusion
- Drug interactions with CYP2C8 inhibitors and inducers
- Protect vials from light at all times - ensure the protective wrap around label is covering the entire vial

https://uptravi.com

Tadalafil (Tadliq)

- PDE5 inhibitor indicated for the treatment of pulmonary arterial hypertension
- Oral Suspension: 20 mg/5 mL
- Dose is 40 mg (10 mL) once daily, with or without food
  - Use with ritonavir requires dosage adjustments
  - Dose adjustment with hepatic or renal dysfunction

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214522s000lbl.pdf

Nalmefene

- (Revex) withdrawn from market in 2008, now returns as generic
- Opioid antagonist
- 2 mg/2ml single dose vials for IV, IM, or SC use
- T ½ is 10.8 hours vs 1-2 hours for naloxone
  - Could precipitate prolonged period of withdrawal
- No new clinical trials were required for FDA approval of generic
- Paucity of data for fentanyl overdose
- Naloxone is safer choice

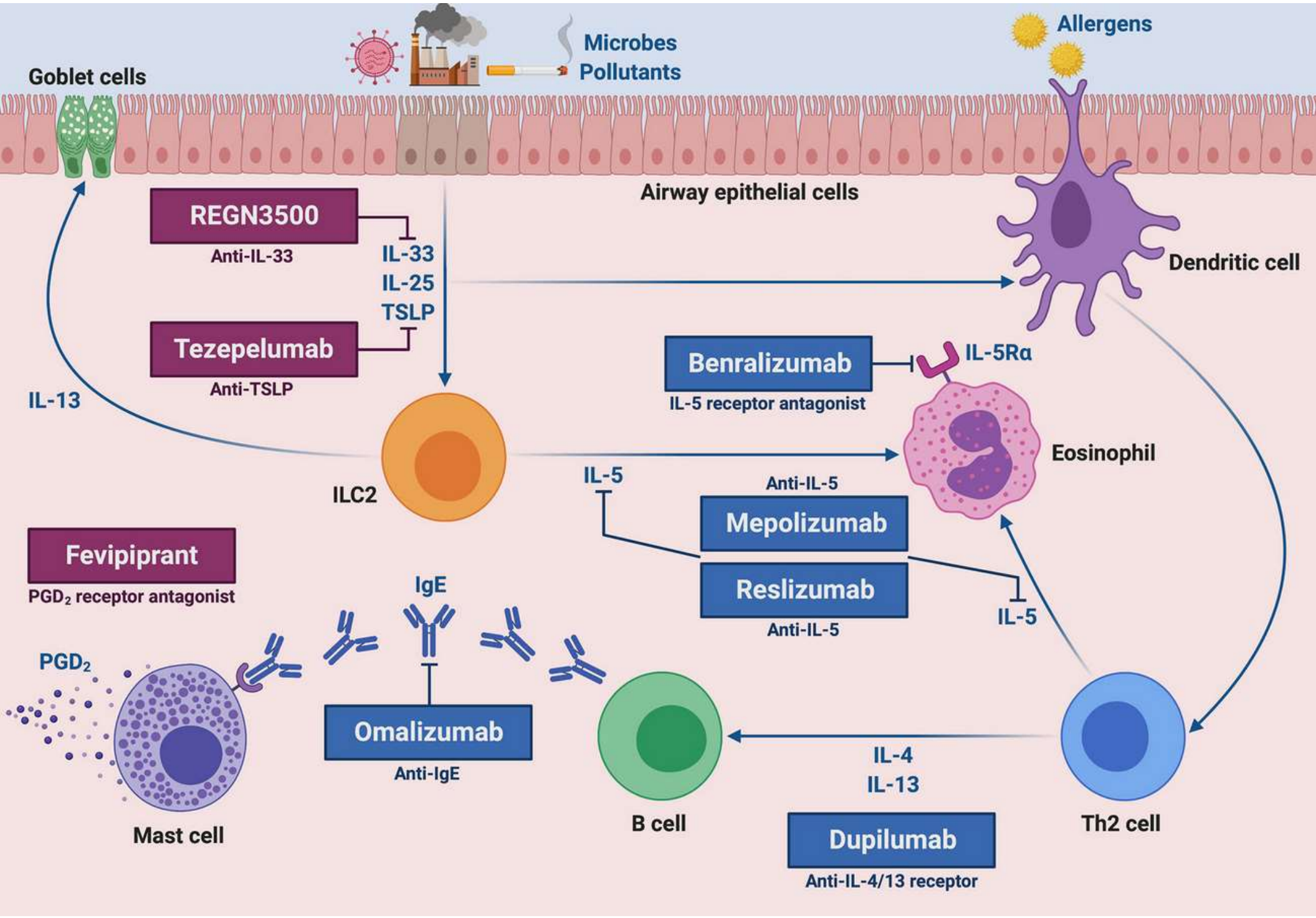
Opioid Reversal Options

Agent	Formulation	Dosage
Nalmefene	2 mg/ml vials	0.5 mg/70 kg IV
Naloxone	0.4 mg/ml vials, syringes; 2 mg/2 ml syringes	0.4-2 mg IV, IM, or SC
Naloxone (Zimhi)	5 mg/0.5 ml syringes	5 mg IM or SC
Naloxone	4 mg/0.1 ml nasal spray	4 mg intranasally
Naloxone (Kloxxado)	8 mg/0.1 ml nasal spray	8 mg intranasally

Tezepelumab (Tezspire)

- SC thymic stromal lymphopoietin (TSLP) blocker approved for add-on maintenance treatment of severe asthma in patients ≥ 12 years old
  - Binds to TSLP, reducing biomarkers and cytokines associated with inflammation
- First biologic approved for treatment of severe asthma without phenotypic or biomarker limitations and the first TLP blocker
- Adverse effects: pharyngitis, arthralgia, back pain
- Dose is 210 mg SC administered by health care professional once every 4 weeks
- Improves lung function and reduces exacerbations in adolescents and adults with severe uncontrolled asthma, regardless of blood eosinophil levels

https://www.tezspire.com



Pelaia C et al. Front. Immunol 2020;11:603312

Bupivacaine/Meloxicam (Zynrelef)

- Single-dose for intraoperative, soft-tissue or periarticular instillation to provide postsurgical analgesia for up to 72 hours in adults undergoing foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures
- Applied without a needle into the surgical site following final irrigation and suction prior to suturing
- The new ER solution comes in contact with moist tissue and becomes viscous and adheres to the site
- Reduced postsurgical pain scores and opioid consumption for 72 hours compared to placebo and bupivacaine HCl alone in clinical trials

https://zynrelef.com/

Bupivacaine/Meloxicam (Zynrelef)

- Dose and administration
  - Supplied as 29.25 mg/mL bupivacaine and 0.88 mg/mL of meloxicam in single dose vials
  - For foot and ankle surgical procedures, such as bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam
  - For small-to-medium open abdominal surgical procedures, such as open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam
  - For lower extremity total joint arthroplasty surgical procedures, such as total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam
- Most common adverse effects (≥10%) are constipation, vomiting, and headache
- Lacks efficacy comparison to liposomal bupivacaine (Exparel)

https://zynrelef.com/

Tocilizumab (Actemra)

- **Interleukin-6 (IL-6) receptor antagonist indicated for treatment of:**
  - **Rheumatoid Arthritis (RA)**
    - **Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)**
  - **Giant Cell Arteritis (GCA)**
    - **Adult patients with giant cell arteritis**
  - **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)**
    - **Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)**
  - **Polyarticular Juvenile Idiopathic Arthritis (PJIA)**
    - **Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis**
  - **Systemic Juvenile Idiopathic Arthritis (SJIA)**
    - **Patients 2 years of age and older with active systemic juvenile idiopathic arthritis**
  - **Cytokine Release Syndrome (CRS)**
    - **Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome**

https://www.gene.com/download/pdf/actemra_prescribing.pdf

Tocilizumab (Actemra) Dose

- **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)**
  - **Recommended Adult Subcutaneous Dosage**
    - **Adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection**

https://www.gene.com/download/pdf/actemra_prescribing.pdf

Terlipressin (Terlivaz)

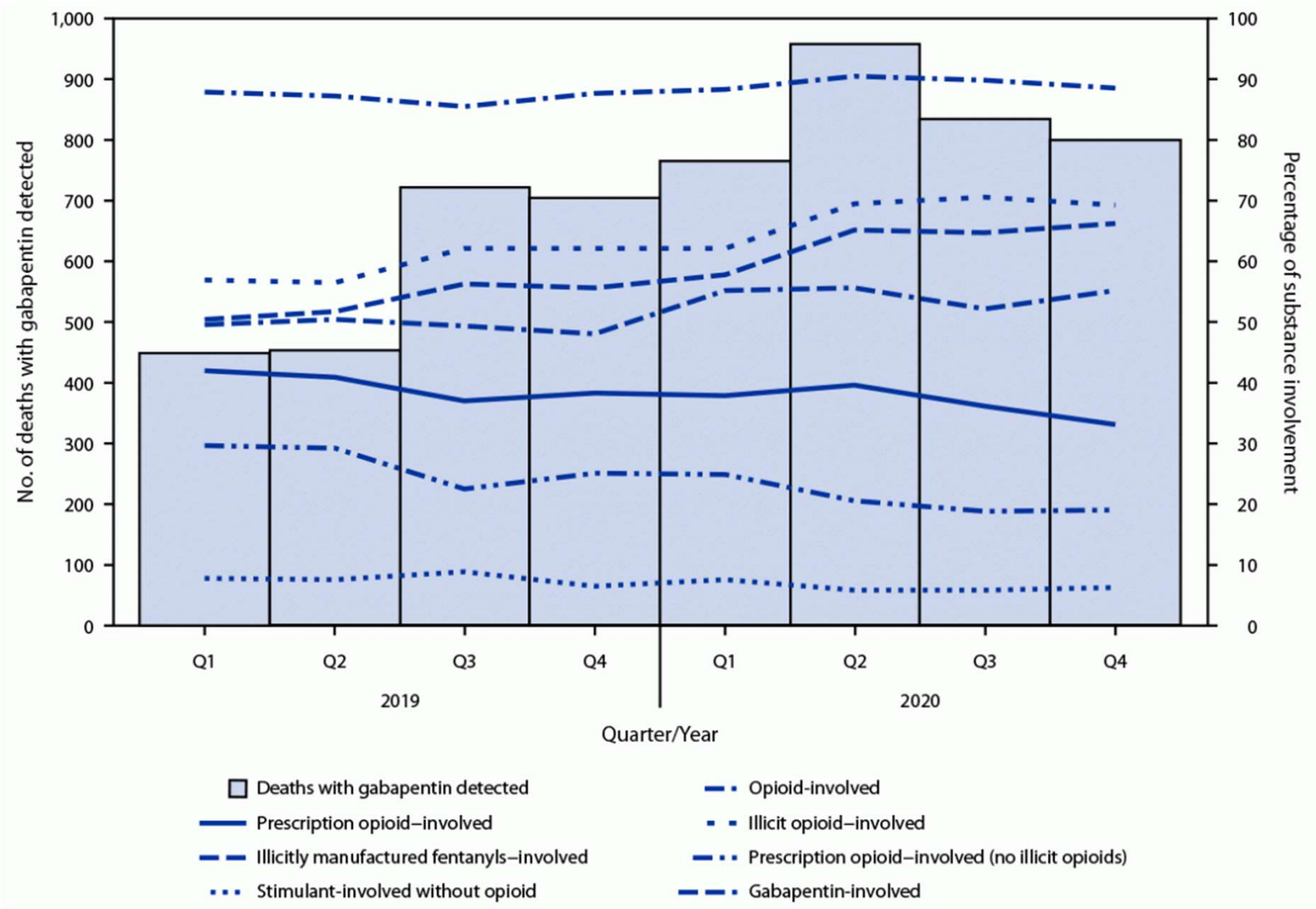
- Vasopressin receptor agonist used to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function
- Approved for use outside of USA for more than 30 years
- Recommended by American College of Gastroenterology guidelines
- Phase 3 Confirm trial evaluated safety and efficacy in HRS type 1
- Recommended Dosage Regimen
  - Days 1 to 3 administer 0.85 mg (1 vial) intravenously every 6 hours.
  - Day 4: Assess serum creatinine (SCr) versus baseline
    - If SCr ↓ by at least 30% from baseline, continue 0.85 mg IV every 6 hours
    - If SCr ↓ by less than 30% from baseline, dose may be increased to 1.7 mg IV every 6 hours
- Boxed Warning: SERIOUS OR FATAL RESPIRATORY FAILURE
- The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea

Gabapentin

- Approved in 1993 for seizures, postherpetic neuralgia in 2002
- 2004 – Pfizer paid a penalty for improper marketing of Neurontin for off label uses
- 2004 generic available
- Prescribing has steadily increased, in 2021 → 6th most common prescribed medication
- Gabapentin withdrawal syndrome
- Medwatch for respiratory depression
- Should gabapentin be classified as a controlled substance?
  - AL, KY, MI, ND, TN, VA, and WV

JAMA Intern Med 2019;179:695-701, JAMA 2022;327:2387, Neurology Today April 21, 2022

Trends in Gabapentin Detection and Involvement in Drug Overdose Deaths - 23 States and the District of Columbia, 2019–2020



MMWR Morb Mortal Wkly Rep 2022;71:664–666

Melatonin Safety Concern

- Increased use in children and adults
- Adults using > 5 mg
- Sales of $821 million in 2020
- Childhood poisonings – lack childproof packaging
- American Academy of Sleep Medicine recommends not using melatonin for insomnia in adults or children
  - Effect upon body temperature, blood sugar, vessel tone
  - Lack of FDA oversight – quality control and content
  - Interferes with puberty in children

JAMA July 21 2022, MMWR 2022 June 3, 71:664–666, Chest Physician May 2022

Asthma Drugs in Pipeline

- Mastinib (AB Science)
  - Oral tyrosine kinase inhibitor that selectively targets mast cells involved in mucus production and airway inflammation
- Depemokimab (GSK)
  - Long-acting IL-5 inhibitor for eosinophilic asthma, dosed every 6 months
- Albuterol/Budesonide (AZ, Avillion) for rescue
- Ecleralimab (Novartis), TSLP inhibitor

Managed Healthcare Executive June 2022

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2022 VOL. 386 NO. 22

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

- **PT027 is an inhaled, fixed-dose combination of albuterol, a short-acting beta2-agonist, and budesonide, an inhaled corticosteroid (ICS)**
- **The NDA submission is supported by data from the multicenter, randomized, double-blind, parallel-group phase 3 MANDALA trial (ClinicalTrials.gov Identifier: NCT03769090), which evaluated the efficacy and safety of albuterol/budesonide, used as an as-needed rescue medicine, on the time to first severe asthma exacerbation in 3132 patients aged 4 years and older with moderate to severe asthma who were receiving ICS with or without additional medications**

RESEARCH SUMMARY

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Papi A et al. DOI: 10.1056/NEJMoa2203163

CLINICAL PROBLEM

Patients typically treat acute asthma symptoms with short-acting β_2-agonist (SABA) rescue therapy. However, SABAs do not treat inflammation, leaving patients at risk for severe exacerbations. Whether rescue therapy with a fixed-dose combination of a SABA (albuterol) plus a glucocorticoid (budesonide) can improve outcomes is unknown.

CLINICAL TRIAL

Design: A multinational, phase 3, double-blind, randomized trial evaluated the safety and efficacy of as-needed use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, in patients with uncontrolled moderate-to-severe asthma receiving inhaled glucocorticoid-containing maintenance therapy.

Intervention: Adults and adolescents were randomly assigned to receive, on an as-needed basis, 180 μg of albuterol plus 160 μg of budesonide, 180 μg of albuterol plus 80 μg of budesonide, or 180 μg of albuterol; the treatments were delivered through a single metered-dose inhaler. Children 4 through 11 years of age were assigned only to the lower-dose combination group or the albuterol-alone group. Participants continued their baseline glucocorticoid-containing maintenance therapies. The primary efficacy end point was the first severe asthma exacerbation in a time-to-event analysis.

RESULTS

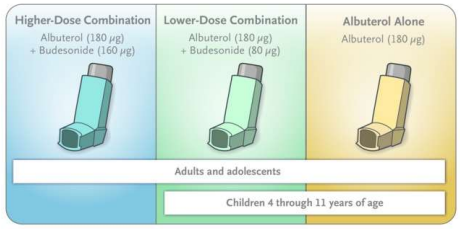
Efficacy: 3123 patients were assessed with respect to the efficacy end points. During a minimum follow-up of 24 weeks, the higher-dose combination of albuterol–budesonide significantly reduced the risk of severe asthma exacerbations, as compared with albuterol alone. The difference between the lower-dose combination and albuterol alone was not significant.

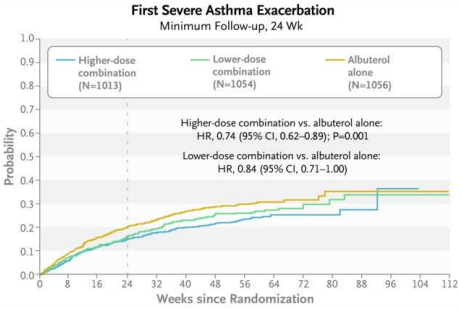
Safety: The incidence of adverse events was similar across the three trial groups.

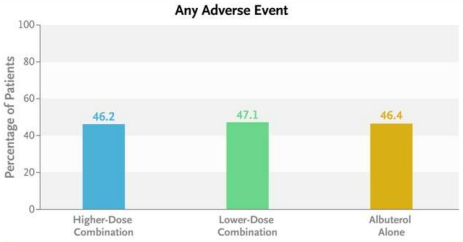
LIMITATIONS AND REMAINING QUESTIONS

- The fraction of exhaled nitric oxide level was not measured, a limitation that precludes direct assessment of antiinflammatory effects.
- A small number of children 4 to 11 years of age were included; thus, no conclusions in this age group could be drawn.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

Among patients with uncontrolled moderate-to-severe asthma receiving inhaled glucocorticoid-containing maintenance therapy, as-needed use of 180 μg of albuterol plus 160 μg of budesonide reduced the risk of severe asthma exacerbations, as compared with albuterol alone, without increasing the incidence of adverse events.

Audience Question #4

- What is the recent approved dosage form for varenecline (Tyrvaya)?

- A. Injection
- B. Nasal spray
- C. Oral disintegrating tablet
- D. Topical patch

Audience Question #5

- What is the dose of naloxone (Kloxxado) ?

- A. 2 mg SC
- B. 4 mg intranasally
- C. 5 mg IM
- D. 8 mg intranasally

Audience Question #6

- Although gabapentin is generally considered safe and is infrequently associated with overdose on its own, when used with other CNS depressants such as opioids, there is a risk for respiratory depression, potentially resulting in death?

- A. True
- B. False

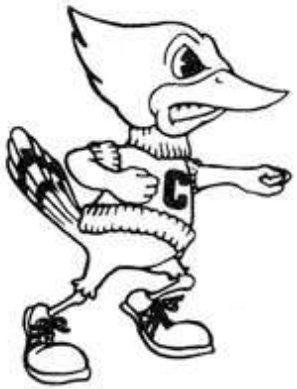
The End

1924

1941

1955

1957



1970

1972

2013