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New Drugs and Drug News of 2019

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Pharmacy practitioners need to be knowledgeable about new drugs introduced to the market, and public health advisories about drug therapy. This webinar will discuss new drugs and news approved in 2019.

Learning Objectives

Pharmacist

1. Recognize the approved indication, common adverse effects and drug interactions for new drugs approved by the FDA in 2019.
2. For each new medication approved in 2019, identify the burden-to-benefit ratio of therapy.
3. Identify important drug alerts by the FDA (Public Health Advisories) and implications for patient care.

Pharmacy Technician

1. Recognize the approved indication, common adverse effects and drug interactions for new drugs approved by the FDA in 2019.
2. For each new medication approved in 2019, identify the burden-to-benefit ratio of therapy.
3. Identify important drug alerts by the FDA (Public Health Advisories) and implications for patient care.

Nurse

1. Recognize the approved indication, common adverse effects and drug interactions for new drugs approved by the FDA in 2019.
2. For each new medication approved in 2019, identify the burden-to-benefit ratio of therapy.
3. Identify important drug alerts by the FDA (Public Health Advisories) and implications for patient care.

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Target Audience

Pharmacists, Pharmacy Technicians, Nurses

Universal Activity Number

Pharmacist	Pharmacy Technician	Nurse
0798-0000-20-004-L01-P	0798-0000-20-004-L01-T	0798-0000-20-004-L01-N

Credit Hours

1.5 Hour

Activity Type

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NEW DRUGS AND DRUG NEWS OF 2019

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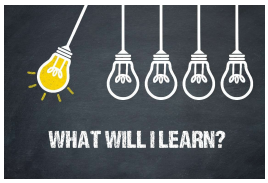
LEARNING OBJECTIVES

- At the conclusion of this program, the participant will be able to:
  - Recognize the approved indication, common adverse effects and drug interactions for new drugs approved by the FDA in 2019.
  - For each new medication approved in 2019, identify the burden-to-benefit ratio of therapy.
  - Identify important drug alerts by the FDA (Public Health Advisories) and implications for patient care.



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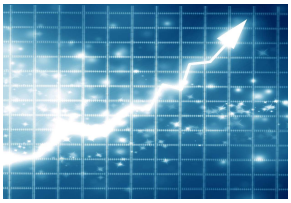
2019 NEW DRUG APPROVALS

- A big year, not quite as big as 2018!
- US Regulators approved a total of FIFTY-TWO drugs
  - 2018 was 61



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BIOSIMILARS

- What IS a biosimilar?
  - A medication similar to an already-authorized biologic medication
    - A biologic drug is a product that is produced from living organisms or contain components of living organisms (human, animal of microorganism).
      - Composed of sugars, proteins, nucleic acids, or complex combinations of these
      - May be living entities such as cells and tissues
    - Vaccines, blood and blood components, allergenics, somatic cells, gene therapies, tissues and recombinant therapeutic proteins
- Why not just develop a generic?

https://www.raps.org/regulatory-focus/news-articles/2016/8/regulatory-explainer-everything-you-need-to-know-about-biosimilars

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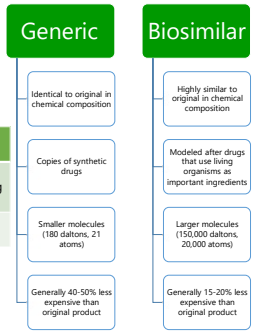
BIOSIMILARS

- Why not just develop a generic?

Proprietary Name	Non-proprietary Name	Indication
Zarxio	Filgrastim-sndz (2015)	To prevent infection during chemotherapy
Mvasi	Bevacizumab-awwb (2017)	Cancer treatment

- What's with those goofy name extension abbreviations?



https://www.cancercenter.com/community/blog/2018/12/whats-the-difference-biosimilar-and-generic-drugs

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BIOSIMILARS APPROVED IN 2019

Generic	Trade	Biosimilar to…	Indication
Adalimumab-afzb	Abrilada	Humira	Arthritis, ulcerative colitis, plaque psoriasis
Adalimumab-bwwd	Hadlima	Humira	Arthritis, ulcerative colitis, plaque psoriasis
Etanercept-ykro	Eticovo	Enbrel	Arthritis, plaque psoriasis
Rituximab-pvvr	Ruxience	Rituxan	Non-Hodgkin's lymphoma, CLL, others
Trastuzumab-anns	Kanjinti	Herceptin	Breast and gastric cancer
Trastuzumab-dttb	Ontruzant	Herceptin	Breast, gastric, gastroesophageal junction cancer
Trastuzumab-qyyp	Trazimera	Herceptin	Breast, gastric, gastroesophageal junction cancer
Pegfilgrastim-bmez	Ziextenzo	Neulasta	To decrease incidence of infection/febrile neutropenia
Bevacizumab-bvzr	Mvasi	Avastin	Various metastatic cancers (in combination with other chemotherapeutic agents)

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ANTIMICROBIALS

Generic	Trade	Indication
Cefiderocol	Fetroja	To treat complicated UTIs in patients who have limited or no alternative treatment options
Imipenem/cilastatin/ relebactam	Recarbrio	To treat complicated urinary tract and complicated intraabdominal infections
Lefamulin	Xenleta	To treat adults with community-acquired bacterial pneumonia
Triclabendazole	Egaten	To treat fascioliasis, a parasitic infection caused by two species of flatworms or trematodes that mainly affect the liver, sometimes referred to a "liver flukes"

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CHEMOTHERAPY

Generic	Trade	Indication
Alpelisib	Piqray	To treat breast cancer
Darolutamide	Nubeqa	To treat adult patients with non-metastatic castration resistant prostate cancer
Enfortumab vedotin-ejfx	Padcev	To treat refractory bladder cancer
Entrectinib	Rozlytrek	To treat adult patients with metastatic non-small cell lung cancer whose tumors are ROS1-positive. To treat adult and pediatric patients 12 years and older with solid tumors.
Erdafitinib	Balversa	To treat adult patients with locally advanced or metastatic bladder cancer
Fam-trastuzumab deruxtecan-nxki	Enhurtu	To treat metastatic breast cancer

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CHEMOTHERAPY

Generic	Trade	Indication
Fedratinib	Inrebic	To treat adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis
Pexidartinib	Turalio	To treat adult patients with symptomatic tenosynovial giant cell tumor
Polatuzumab	Polivy	To treat adult patients with relapsed/refractory diffuse large B cell lymphoma
Selinexor	Xpovio	To treat patients with relapsed or refractory multiple myeloma
Zanubrutinib	Brukinsa	To treat mantle cell lymphoma, a form of blood cancer

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DERMATOLOGY

Generic	Trade	Indication
Prabotulinumtoxin A-xvfs	Jeuveau	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Risankizumab-rzaa	Skyrizi	To treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Trifarotene	Aklief	For facial and truncal acne vulgaris in patients 9 years or older

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PRABOTULINUMTOXINA (JEUVEAU)

- Approved for temporary improvement in the appearance of moderate to severe glabellar lines (frown lines)
- Fourth botulinum toxin approved in US
- Similar in efficacy to onabotulinumtoxin A (Botox Cosmetic)
- Adverse effects – headache, eyelid ptosis, URI, increased WBC
- Given IM at five glabellar sites; at least 3 months between treatments
- $610 per treatment

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RISANKIZUMAB (SKYRIZI)

- Interleukin (IL)-23 antagonist risankizumab-rzaa (Skyrizi) for treatment of moderate to severe plaque psoriasis in adults.
  - Third IL-23 antagonist approved (guselkumab [Tremfya], tildrakizumab [Ilumya])
  - IL-23 is a cytokine involved in normal inflammatory and immune responses
  - The p19 and p40 subunits of IL-23 are overexpressed in psoriatic lesions
- Risankizumab is a humanized monoclonal IgG1 antibody that selectively binds to the p19 subunit of IL-23, inhibiting it from binding to the IL-23 receptor and preventing downstream release of pro-inflammatory cytokines and chemokines

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RISANKIZUMAB CLINICAL TRIALS

Regimen	sPCA 0 or 1	PASI 90	PASI 100
IMMHANCE (n = 507, week 16 results)			
Risankuzumab 150 mg	84%	73%	47%
Placebo	7%	2%	1%
ULTIMMA -1 (n = 506, week 16 results)			
Risankizumab 150 mg	87.8%	75.3%	35.9%
Ustekinumab 45 or 90 mg	63.0%	42.0%	12.0%
Placebo	7.8%	4.9%	0%
ULTIMMA-2 (n = 491; week 16 results)			
Risankizumab 150 mg	83.5%	74.8%	50.7%
Ustekinumab 45 or 90 mg	61.6%	47.5%	24.2%
Placebo	5.1%	2.0%	2.0%
IMMVENT (n = 605)			
Risankizumab 150 mg	83.7%	72.4%	39.9%
Adalimumab 40 mg	60.2%	47.4%	23.0%

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RISANKIZUMAB (SKYRIZI)

- Adverse effects – 22.1% treated patients in first 16 weeks (vs. 14.7% of those treated with placebo)
  - URI, headache, fatigue
  - Injection site reactions, tinea infections
- Dosage and Administration
  - Carton contains 2 single-dose risankizumab 75 mg/0.83 ml prefilled syringes
  - Dose is 150 mg (two 75-mg injections) SC at weeks 0 and 4, then every 12 weeks
  - Refrigerate syringes, allow to sit at room temperature 30 minutes

Approximately $60,000/year

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TRIFAROTENE (AKLEIF)

- Trifarotene 0.005% cream – indicated for the topical treatment of facial and truncal acne vulgaris in patients 9 years of age or older
- Trifarotene is an agonist of retinoic acid receptors
  - With particular activity at the gamma subtype of RAR
  - Stimulating this receptor results in target genes which are associated with cell differentiation and inflammation
- Adverse effects – application site irritation, application site pruritus and sunburn
- Use a moisturizer as needed with initiation of therapy

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TRIFAROTENE (AKLEIF)

	Trifarotene	Placebo
Study 1		
Facial Acne	29.4% success at 12 weeks	19.5% success at 12 weeks
Truncal Acne	37.5% success at 12 weeks	25.0% success at 12 weeks
Study 2		
Facial Acne	35.7% success at 12 weeks	25.7% success at 12 weeks
Truncal Acne	42.6% success at 12 weeks	29.9% success at weeks

Success = a score of 1 (almost clear) or 0 (clear) and at least a 2-grade improvement from baseline to Week 12

45 gram tube costs $554.30

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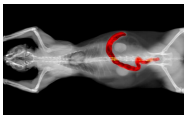
IMAGING

Generic	Trade	Indication
Air polymer type A	EsEm Foam	Diagnostic agent used to assess fallopian tube patency (openness) in women with known or suspected infertility
Fluorodopa F 18		Diagnostic agents for PET scan with suspected Parkinson's disease
Ga-68-DOTATOC	GA-68-DOTATOC	For use with PET for localization of somatostatin receptor positive neuroendocrine tumors



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NEUROLOGIC/PSYCHIATRIC

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NEUROLOGIC/PSYCHIATRIC

Generic	Trade	Indication
Brexanlone	Zulresso	To treat postpartum depression in adult women
Golodirsen	Vyondyx 53	To treat Duchenne muscular dystrophy (certain patients)
Onasemnogene abeparvovec	Zolgensma	Recombinant AAV9-based gene therapy for gene encoding human survival motor neuron protein (spinal muscular atrophy)
Istradefylline	Nourianz	To treat adult patients with Parkinson's disease experiencing "off" episodes
Inbrija	Acorda	Oral inhaled dry-powder formulation of levodopa, for intermittent treatment of "off" episodes in Parkinson's patients being treated with carbidopa/levodopa
Lasmiditan	Reyvow	For the acute treatment of migraine with or without aura in adults
Ubrogepant	Ubrelvy	Acute treatment of migraine with or without aura in adults

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NEUROLOGIC/PSYCHIATRIC

Generic	Trade	Indication
Lemborexent	Dayvigo	For the treatment of insomnia
Pitolisant	Wakix	To treat excessive daytime sleepiness in adult patients with narcolepsy
Solriamfetol	Sunosi	To treat excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea
Lumateperone	Caplyta	For the treatment of schizophrenia
Siponomod	Mayzent	To treat adults with relapsing forms of multiple sclerosis
Cenobamate	Xcopri	To treat partial onset seizures

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BREXANOLONE (ZULRESSO)

- Indicated for the treatment of postpartum depression in adult woman (first in class); affects up to 20% of women after childbirth
- Brexanolone is an analogue of the endogenous human hormone allopregnanolone, which is a $GABA_A$ receptor modulator
  - Allopregnanolone abruptly dips around childbirth – may lead to PPD
- Given IV as an infusion over 2.5 days following a titration schedule
  - Given by a healthcare provider in a certified healthcare facility under close monitoring (requires continuous pulse oximetry and assessment of sedation every 2 hours during waking hours due to sudden LOC; there is a REMS in place)
  - Do not administer to patients with end-stage renal disease

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BREXANOLONE (ZULRESSO)

- Clinical trials – primary outcome was the mean change from baseline in depressive symptoms as measured by HAM-D total score at hour 60 (end of infusion).
- Both studies – brexanolone (titrated to target dose of 90 mcg/k/h) was modestly superior to placebo
- Adverse effects – sleepiness, dry mouth, loss of consciousness, flushing

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Table 3: Results for the Primary Endpoint – HAM-D Total Score (Studies 1 and 2)

Study Number	Treatment Group (# ITT subject)	Primary Endpoint: Change from Baseline in HAM-D Total Score at Hour 60		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI) Unadjusted p-value
1	ZULRESSO target dosage 90 mcg/kg/hour (n=41)*	28.4 (2.5)	-17.7 (1.2)	-3.7 (-6.9, -0.5) P=0.0252
	Placebo (n=43)	28.6 (2.5)	-14.0 (1.1)	
	ZULRESSO target dosage 60 mcg/kg/hour (n=38)*	29.0 (2.7)	-19.5 (1.2)	-5.5 (-8.8, -2.2) P=0.0013
	Placebo (n=43)	28.6 (2.5)	-14.0 (1.1)	
2	ZULRESSO target dosage 90 mcg/kg/hour (n=51)*	22.6 (1.6)	-14.6 (0.8)	-2.5 (-4.5, -0.5) P=0.0160
	Placebo (n=53)	22.7 (1.6)	-12.1 (0.8)	

HAM-D: Hamilton depression rating scale; ITT: intention to treat; SD: standard deviation; LS: least squares; SE: standard error; CI: confidence interval; *: statistically significant after multiplicity adjustments

https://assets.sagerx.com/zulresso/prescribing-information.pdf

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BREXANOLONE (ZULRESSO)

- Dosing:
  - Hours 0-4 → 30 mcg/kg/hr
  - Hours 4-24 → 60 mcg/kg/hr
  - Hours 24-52 → 90 mcg/kg/hr
  - Hours 52-56 → 60 mcg/kg/hr
  - Hours 56-60 → 30 mcg/kg/hr
- Modestly more effective than placebo in reducing post-infusion depressive symptoms in women with moderate to severe postpartum depression.
- Durability of its antidepressant effect is unclear.
- Not approved to use before delivery.

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SIPONIMOD (MAYZENT)

- A sphingosine 1-phosphate receptor modulator; oral
- Second in class (first was fingolimod [Gilenya])
- Indications include:
  - Relapsing forms of multiple sclerosis
  - Clinically isolated syndrome (initial neurological episode)
  - Relapsing-remitting disease
  - Active secondary progressive MS
- MOA – module S1P receptors, prevents lymphocyte egress from lymph nodes into peripheral blood and reduced T-cell infiltration into the CNS

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SIPONIMOD (MAYZENT)

- Approval based on a study with 1651 patients with secondary progressive MS
- Siponimod reduced risk of 3-month confirmed disability progression by 21% compared to placebo.
  - Also showed reduction in annualized relapse rate
  - No significance shown in non-active SPMS patients
- Determine CYP2C9 genotype before initiation
- Contraindicated in 2C9/*3/*3, recent (within 6 mo) MI, unstable angina, CVA, TIA, decompensated HF, Class III/IV HF, Mobitz Type II 2nd/3rd degree heart block or sick sinus syndrome (unless paced)

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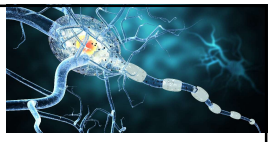
SIPONIMOD (MAYZENT)



- Warnings
  - Risk of bradycardia, AV conduction delays
  - Increased risk of infections (may be fatal)
  - Immunosuppression
  - Diabetes/history of uveitis (increased risk macular edema)
  - Increased LFTs, hepatic dysfunction, respiratory dysfunction
- Many interactions (QT prolonging drugs, drugs causing bradycardia, live virus vaccines), many other drugs
- But what a deal compared to fingolimod ($99,896/year)
- Siponimod is ONLY $88,500/year!

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FDA WARNING - GABAPENTIN

- FDA has issued an alert about "life-threatening" breathing difficulties in patients who use gabapentin or pregabalin:
  - With opioids or other drugs that depress the CNS
  - Patients with underlying respiratory impairment
  - The elderly
- Between January 1, 2012 and October 27, 2017 there were 49 cases of respiratory depression reported with the use of gabapentinoids (15 with gabapentin, 34 with pregabalin)
  - In 92% of cases, patient either had a respiratory risk factor or were using a concomitant CNS depressant
  - 12 deaths reported
- New labeling added; consider risk factors, monitor patient closely, dose reduce with renal impairment and risk factors, or if respiratory depression occurs

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INBRIJA (ACORDA)

- Orally inhaled drug powder formulation of levodopa, for intermittent treatment of "off" episodes in patients with Parkinson's disease being treated with carbidopa/levodopa.
- Options to treat "off" episodes include:
  - More frequent dosing of carbidopa/levodopa
  - Use of extended-release carbidopa/levodopa
  - Addition of a dopamine agonist or a catechol-O-methyltransferase (COMT) or monoamine oxidase type B (MAO-B) inhibitor
- Dose is 84 mg inhaled up to 5 times a day as needed
- Time to maximum effect ~ same as IR levodopa tablet (0.5 hours)

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INBRIJA (ACORDA)

- Clinical trials showed Inbrija more effective than placebo for intermittent treatment of "off" episodes
- Has not been compared to other therapeutic options
- May be best positioned in patients with severely delayed gastric emptying who require a non-oral drug for prn treatment
- Adverse effects –
  - Cough (15%), URI (6%), sputum discoloration (5%), nausea (5%)
- Cost – for one episode per day the cost is $950.
  - It's indicated to use up to 5 times per day. You do the math.

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ISTRADEFYLLINE (NOURIANZ)

- Approved as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "off" episodes
- In case you were wondering, the chemical name is:
  - (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione
- Istradefylline is an oral selective adenosine A_{2A} receptor antagonist and non-dopaminergic pharmacologic option
  - Receptors found in basal ganglia of the brain where degeneration or abnormality is noted in PD; basal ganglia are involved in motor control
  - Other than that, mechanism of action is unknown

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ISTRADEFYLLINE (NOURIANZ)

- Clinical efficacy – additional "on" time ranges from half an hour to almost an hour a day
- Major adverse effects – dyskinesia, dizziness, constipation, nausea, hallucinations, insomnia.
- One month supply (20 mg or 40 mg) is about $1500

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SOLRIAMFETOL (SUNOSI)

- A dopamine and norephinephrine reuptake inhibitor
- Indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea
- Competitor medications used first line for narcolepsy or OSA; they inhibit dopamine reuptake
  - Modafinil (Provigil)
  - Armodafinil (Nuvigil)
- Sympathomimetic stimulants promote release of norepinephrine and dopamine and inhibit reuptake
  - Mixed amphetamine salts (Adderall)
  - Methylphenidate (Ritalin)

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SOLRIAMFETOL (SUNOSI)

- Approval based on two studies (one with narcolepsy; one with OSA)
- Outcomes were Maintenance of Wakefulness Test and the Epworth Sleepiness Scale
  - Narcolepsy trial – MWT and ESS improved significantly in 150 mg group and 300 mg group, but not 75 mg group
  - In the OSA trial, MWT and ESS changes were significant in all tx groups
- Adverse effects – headache (16%), nausea, anorexia, dry mouth, anxiety, insomnia, increase in BP/HR
- Dose is 75 mg once daily for narcolepsy; 37.5 mg for OSA
  - Can double dose every 3 days to a maximum of 150 mg a day
  - Take on awakening and not within 9 hours before planned sleep

30 TABLETS, 75 OR 150 MG = $650

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PITOLISANT (WAKIX)

- Approved by FDA to treat excessive daytime sleepiness in adults with narcolepsy
- MOA – H3 receptor antagonist/inverse agonist
  - First in class
  - Acts on histamine H3 receptors – binds to presynaptic H3 autoreceptors, preventing histamine from binding to these receptors (antagonist effect)
  - This binding also results in increased histamine synthesis and release (inverse agonist effect)
  - Also enhances other neurotransmitters in the brain (dopamine, acetylcholine, noradrenaline)

https://wakixhcp.com/mechanism-of-action/

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PITOLISANT (WAKIX)

- Clinical trials – measured Epworth Sleepiness Scale – showed significant improvement
- Adverse effects – insomnia, nausea, anxiety
- Dose
  - 8.9 mg once daily for 1 week
  - Then increase to 17.8 mg once daily
  - May increase to 35.6 mg once daily
- Cost – 17.8 mg, 30 tablets = $5,600

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LEMBOREXANT (DAYVIGO)

- An orexin receptor antagonist, approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adult patients
- Efficacy
  - Significant in both sleep onset and sleep maintenance variables vs. placebo and vs. zolpidem XR
  - Significant at both 5 and 10 mg dose in subjective sleep onset latency vs. placebo. Also improved subjective sleep efficiency and subjective wake after sleep onset vs. placebo

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LEMBOREXANT (DAYVIGO)

- Primary adverse effect – somnolence
- Dose – 5 mg taken no more than once at night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. May be increased to 10 mg.

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FDA APPROVED ORAL FORMULATION

- FDA approved an oral film formulation of riluzole (Exservan)
- Treatment of amyotrophic lateral sclerosis (ALS)
- Administered twice daily, without water
- Product demonstrates bioequivalence to the reference drug (Rilutek)
- Last year FDA approved a liquid formulation of riluzole (Tiglutik) which is administered by oral syringe

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LUMATEPERONE (CAPLYTA)

- An atypical antipsychotic agent indicated for the treatment of schizophrenia in adult patients
- MOA unknown but effect thought to be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors
- Demonstrated efficacy in the baseline to Day 28 Positive and Negative Syndrome Scale

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LUMATEPERONE (CAPLYTA)

- Adverse effects – weight gain, increased fasting glucose, increased triglycerides and total cholesterol.
  - Incidence of EPS was 6.7% (vs. 6.3% with placebo)
- Carries black box warning about increased mortality in elderly patients with dementia-related psychosis

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LASMIDITAN (REYVOW)

- Approved for the acute treatment of migraine with or without aura in adults
- Mechanism – a serotonin (5-HT) 1F receptor agonist
- Showed significantly more patients were migraine pain-free 2 hours following the first dose vs. placebo
- Second end point was relief from most bothersome symptom at 2 hours (e.g., photophobia, phonophobia, nausea)
- Adverse effects – dizziness, fatigue, paresthesia, sedation
  - Do not drive or operate machinery for at least 8 hours after dosing
- Dose – 50, 100 or 200 mg taken no more than once daily

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LASMIDITAN (REYVOW)

	Study 1			Study 2			
	REYVOW 100 mg	REYVOW 200 mg	Placebo	REYVOW 50 mg	REYVOW 100 mg	REYVOW 200 mg	Placebo
Pain Free at 2 hours							
N	498	503	515	544	523	521	534
% Responders	28.3	31.8	15.3	28.3	31.4	38.8	21.0
Difference from placebo (%)	13	16.5		7.3	10.4	17.8	
p-value	<0.001	<0.001		0.006	<0.001	<0.001	
MBS Free at 2 hours							
N	464	467	480	502	491	478	509
% Responders	41.2	40.7	29.6	40.8	44.0	48.7	33.2
Difference from placebo (%)	11.6	11.1		7.6	10.8	15.5	
p-value	<0.001	<0.001		0.014	<0.001	<0.001	

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211280s000lbl.pdf

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LASMIDITAN (REYVOW)

- Will be a scheduled product
- Because "I love you more than placebo, but not as much as alprazolam!"

52

UBROGEPANT (UBRELVY)

- Approved for acute treatment of migraine with or without aura in adults
- First ORAL calcitonin gene-related peptide (CGRP) receptor antagonist
- Adverse effects – nausea and somnolence
- Use is contraindicated with strong CYP3A4 inhibitors
- Dose – 50 or 100 mg taken orally; second dose may be taken at least 2 hours after initial dose
  - Maximum of 200 mg in 24 hours)

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	Study 1			Study 2	
	UBRELVY 50 mg	UBRELVY 100 mg	Placebo	UBRELVY 50 mg	Placebo
Pain Free at 2 hours					
N	422	448	456	464	456
% Responders	19.2	21.2	11.8	21.8	14.3
Difference from placebo (%)	7.4	9.4		7.5	
p value	0.002	<0.001		0.007	
Most Bothersome Symptom Free at 2 hours					
N	420	448	454	463	456
% Responders	38.6	37.7	27.8	38.9	27.4
Difference from placebo (%)	10.8	9.9		11.5	
p value	<0.001	<0.001		<0.001	
Pain Relief at 2 hours					
N	422	448	456	464	456
% Responders	60.7	61.4	49.1	62.7	48.2
p value	<0.001	<0.001		<0.001	
Sustained Pain Freedom 2-24 hours					
N	418	441	452	457	451
% Responders	12.7	15.4	8.6	14.4	8.2
p value	*NS	0.002		0.005	

* Not statistically significant (NS)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210280s000lbl.pdf

54

CENOBAMATE (XCOPRI)

- Approved for partial-onset seizures in adults.
- MOA – unknown but reduces repetitive neuronal firing by inhibiting voltage-gated sodium channels.
- Evaluated as add-on therapy, reduced seizures frequency by about 50% (placebo reduced by about 22%)
- Adverse effects – somnolence, dizziness, fatigue, diplopia, headache.
  - Has been linked to drug reaction with eosinophilia and systemic symptoms
  - Can cause QTc shortening > 20 msec
- Dose 12.5 mg once daily (may titrate up to 400 mg once daily)

55

GOLODIRSEN (VYONDYS 53)

- Approved for the treatment of Duchenne muscular dystrophy with confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping
- Approved based on surrogate end point demonstrating an increase in dystrophin production from 0.10% of normal at baseline to 1.02% of normal after 48 weeks of treatment.
  - FDA states this is "reasonably likely to predict clinical benefit in patients with DMD who have this gene mutation." Trial ongoing through 2024.
- Adverse effects – headache, pyrexia, cough, vomiting, abdominal pain, nasopharyngitis and nausea.
- Dose 30 mg/kg once a week as a 35-60 minute IV infusion.
- Cost probably ~ $300,000 year

56

ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

- Approved for the treatment of children less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron (SMN1) gene
- Effectiveness shown in an open-label, single-arm clinical trial and an ascending-dose clinical trial (also open-label)
- Patients all < 6 months old, with confirmed SMA
- Efficacy established on **basis of survival** (time from birth to either death or permanent ventilation [requiring invasive ventilation or respiratory assistance for > 16 hours per day], **achievement of developmental motor milestones such as sitting without support**

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ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

- Ongoing clinical trial enrolled 21 patients with infantile-onset SMA
- Before enrollment, none required non-invasive ventilator support, all could exclusively feed orally
- All patients received one dose of Zolgensma – 1.1 x 10^{14} vg/kg
- Mean age at enrollment was 3.9 months
- March 2019 – one child died, one withdrew, remaining 19 alive without permanent ventilation

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ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

- Data cutoff – 13/19 continued in trial reached 14 months of age without permanent ventilation
  - 10/21 achieved ability to sit without support for ≥ 30 seconds
    - Based on historical data, patients who met study entry criteria would not be expected to attain the ability to sit without support
    - Only 25% of would have been expected to survive beyond 14 months of age
- Completed clinical trial enrolled 15 patients (3 low dose, 12 high dose). Twenty-four months post infusion:
  - Low dose cohort – one on permanent ventilation. None could sit without support, stand or walk
  - High dose cohort – all alive without permanent ventilation. 9 of 12 able to sit without support for ≥ 30 seconds, and 2 were able to stand and walk without assistance.

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ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

- Adverse effects – vomiting, aminotransferase elevations, acute liver injury, thrombocytopenia, increases in troponin I levels
- Dosage and administration - 1.1 x 10^{14} vector genomes/kg given as a single IV infusion over 60 minutes.
  - Not recommended for premature neonates
  - Systemic corticosteroid is given for a total of 30 days, starting one day before infusion
- Deemed as a LIFE SAVING TREATMENT.
- So….how much IS that doggy in the window? What would YOU pay?

60

ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA)

- Manufactured by AveXis, a pharmaceutical company owned by Novartis. This is the most expensive drug in history.

$2.125 million per patient

- Novartis offers insurers the ability to pay $425,000 a year for five years.
- This is based on an estimate of years of quality of life valued at $100,000 to $150,000 per year. MIND BLOWN!

https://www.npr.org/sections/health-shots/2019/05/24/725494168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever

61

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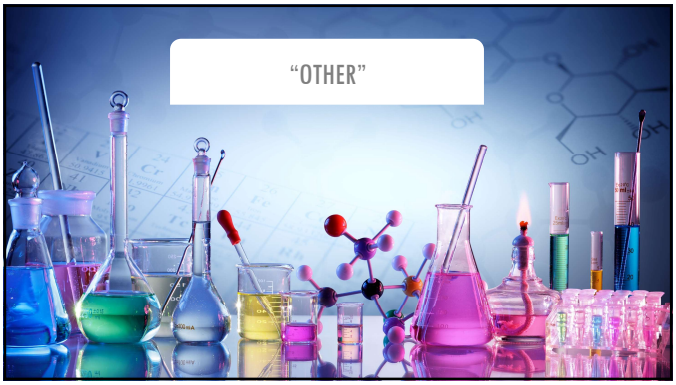
FDA WARNING – INSOMNIA MEDICATIONS

- FDA is adding a new boxed warning on several insomnia medications following reports of serious injuries and death associated with complex sleep behaviors where patients engaged in activities while not fully awake
- Eszopiclone, zaleplon, zolpidem
- Seen with a single dose, or those taking drug for a longer period
- Adverse events – falls (intracranial hemorrhages, vertebral fractures, hip fractures, death), self-injuries, accidental overdoses, hypothermia, suicide attempts, apparent complete suicides, fatal MVAs, gunshot wounds, carbon monoxide poisoning, drowning or near drowning, burns, homicide.

https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warnings-about-rare-serious-problems-related-certain-prescription-insomnia

63



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OTHER

Generic	Trade	Indication
Ferric maltrol	Accrufer	To treat iron deficiency anemia in adults
Givosiran	Giviaari	Acute hepatic porphyria, a rare blood disorder
Luspatercept-aamt	Reblozyl	For the treatment of anemia in adult patients with beta thalassemia who require regular RBC transfusions
Tafamidis meglumine	Vyndaqel	To treat heart disease (cardiomyopathy) caused by transthyretin mediated amyloidosis in adults
Tenapanor	Ibsrela	To treat irritable bowel syndrome with constipation in adults
Upadacitinib	Rinvoq	To treat adults with moderate to severe acute rheumatoid arthritis

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OTHER

Generic	Trade	Indication
Romosozumab-aqqg	Evenity	To treat osteoporosis in postmenopausal women at high risk of fracture
Bremelanotide	Vyleesi	To treat hypoactive sexual desire disorder in premenopausal women
Upadacitinib	Rinvoq	To treat adults with moderate to severe acute rheumatoid arthritis
Crizanlizumab-tmca	Adakveo	Pain complication of sickle cell disease
Voxelotor	Oxbryta	Sickle cell disease

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ROMOSOZUMAB-AQQG (EVENITY)

- A sclerostin inhibitor, is a once-monthly subcutaneous treatment of osteoporosis in postmenopausal women who are at high risk for fracture, or who failed or cannot tolerate other drugs for this indication.
  - Risk of fracture - History of osteoporotic fracture or multiple risk factors for fracture
  - First in class
- Efficacy
  - More effective than oral bisphosphonate alendronate in reducing new vertebral and clinical fractures
  - More effective than the PTH receptor agonist teriparatide in increasing hip BMD

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ROMOSOZUMAB-AQQG (EVENITY)

- Adverse effects – arthralgia, headache, may cause jaw osteonecrosis or atypical fractures
  - Serious adverse cardiovascular events occurred more frequently with romosozumab than with alendronate (2.5% vs. 1.9%)
  - Do not use if patient had MI or stroke within previous year
- Dosage – 210 mg as two 105-mg SC injections at different sites once monthly for a maximum of 12 doses. Start an antiresorptive medication (e.g., alendronate) after stopping romosozumab to maintain BMD
- Cost is $1825/month
- Conclusion – consider for woman at very high risk, but it's expensive and long-term safety data are lacking. Also, increases risk of CV events.

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BREMELANOTIDE (VYLEESI)

- Approved for treatment of premenopausal women with acquired, generalized, hypoactive sexual desire disorder (HSDD) as characterized by:
  - Low sexual desire that causes marked distress or interpersonal difficulty
  - And is not due to:
    - A co-existing medical or psychiatric condition
    - Problems with the relationship
    - The effects of a medication or drug substance
- Melanocortin receptor agonist

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BREMELANOTIDE (VYLEESI)

- Trial with 1247 patients, 80% chose to continue treatment in the open label safety extension study for an additional year, despite 40% incidence of nausea (13% required medication to treat), flushing, injection site reactions, headache, vomiting, and a 3-6 mmHg increase in BP.
- Dose – 1.75 mg/0.3 ml premixed single-dose autoinjector pen 45 minutes prior to anticipated sexual activity
  - Limited to one dose per day to minimize hypertensive effects
  - DC if no effect within 8 weeks
- About $250 a dose

70

UPADACITINIB (RINVOQ)

- A janus kinase inhibitor, approved for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.
- Clinical efficacy – 52% of upadacitinib patients (vs. 28% patients receiving methotrexate) achieved ACR50
  - 68% of patients who were inadequate responders to methotrexate achieved ACR20 endpoint, vs. 41% of those who continued MTX
  - 71% of MTX + upadacitinib achieved ACR20 vs. 36% of MTX only at week 12
- Adverse effects – URI, nausea, cough, pyrexia. BBB for serious infections, malignancy and thrombosis.
- Dose – 15 mg XR once a day

COST $5,000/MONTH

71

ONE FOR THE ROAD. . . (NOT A POLL QUESTION)

- The FDA has required additional warnings be added to the labeling of several medications used to treat insomnia (such as zolpidem) for which of the following reasons?
  - A. Hang-over sedation the next morning
  - B. Complex sleep behaviors (e.g., patients harming themselves and others)
  - C. Paradoxical excitation and exacerbated insomnia in older adults
  - D. Anticholinergic effects such as dry mouth, blurred vision, constipation

72

CRIZANLIZUMAB (ADAKVEO)

- Approved to reduce the frequency of vaso-occlusive crisis (VOC) in patients aged ≥ 16 years with sickle cell disease.
- Humanized IGG2kappa monoclonal antibody that blocks the interactions between endothelial cells, platelets, red blood cells and leukocytes by binding to selectin on the surface of the activated endothelium and platelets.
  - First targeted therapy specifically inhibiting selectin, a substance that contributes to cells sticking together and leads to vaso-occlusive crisis

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CRIZANLIZUMAB (ADAKVEO)

- Efficacy – evaluated in 198 patients with sickle cell disease
  - IV infusion (5 mg/kg) over 30 minutes Weeks 0, 2 and every 4 weeks thereafter for 52 weeks
  - Endpoint – annual rate of VOCs leading to a health care visit
    - Crizanlizumab reduced median annual rate of VOCs by 45% vs. placebo
    - Reduction in VOC frequency was regardless of sickle cell disease genotype and/or hydroxyurea use
  - Adverse effects – nausea (18%), arthralgia (18%), back pain (15%) and pyrexia (11%)

COST BETWEEN $7,000-$10,000/MONTH DEPENDING ON PATIENT WEIGHT

74

VOXELOTOR (OXBRYTA)

- Approved for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.
  - Indication approved under accelerated approval based on increase in hemoglobin; continued approval contingent on clinical benefit from confirmatory trials
- Voxelotor is a sickle hemoglobin polymerization inhibitor that binds to sickle hemoglobin and exhibits preferential partitioning to RBCs
  - Sickle cells are less likely to bind together and form the sickle shape, which can cause low hemoglobin levels due to RBC destruction

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VOXELOTOR (OXBRYTA)

- Clinical trial – 274 patients with SCD (median age 24 yo; median baseline Hb: 8.5 g/dL).
  - Primary endpoint was Hb response rate defined as the proportion of patients with a Hb increase of > 1 g/dl from baseline to Week 24
  - Voxelotor response rate was 51.1% vs. 6.5% for placebo.
  - Adjusted mean change from baseline to Week 24 in Hb was 1.14 g/dL vs. -0.08 g/dL for placebo group
- Adverse effects – headache, diarrhea, abdominal pain, nausea, fatigue, rash, pyrexia
- Dose 1,500 mg once daily

COST $10,500/MONTH

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NEW YORK TIMES

- December 9, 2019
- Pharmaceutical manufacturer argues that without treatment, management of SCD costs about $10,000/year to treat a child; about $30,000/year to treat an adult (pain crises, organ damage, strokes)
  - Does not include disability economic burden


The New York Times

Two New Drugs Help Relieve Sickle-Cell Disease. But Who Will Pay?

Adakveo and Oxbryta could be revolutionary treatments, but each costs about $100,000 per year and must be taken for life.

Red blood cells distorted by sickle-cell disease seen under an electron microscope. The Food and Drug Administration recently approved two new drugs to treat the disease. Omikron/Science Source

https://www.nytimes.com/2019/12/07/health/sickle-cell-drugs-cost.html

77

78

FDA WARNING ABOUT VAPING THC/E-CIGS

- CDC has linked the use of vaping products to more than 1,000 lung injury cases and 18 confirmed deaths
- FDA is warning consumers to stop using e-cigarette or vaping products, particularly those containing tetrahydrocannabinol (THC)
- CDC reports that patients experienced respiratory symptoms such as cough, shortness of breath or chest pain; GI symptoms, fatigue, fever, and weight loss in some patients
  - Radiologic findings included bilateral pulmonary infiltrates and diffuse ground-glass opacities in some patients

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

79

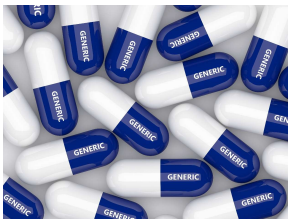
KEEP AN EYE OUT FOR…

- Aducanumab – first therapy that could slow Alzheimer's disease
  - Targets amyloid deposits
  - Clinical trials claim a significant reduction in cognitive decline

80

TALK TO ME, SWEET GENERICS…

- 7 common drugs that will go generic soon…..
  - Pregabalin (Lyrica)
  - Tadalafil (Cialis)
  - Sitagliptin (Januvia)
  - Lubiprostone (Amitiza)
  - Buprenorphine/naloxone (Zubsolv)
  - Varenicline (Chantix)
  - Diclofenac (Zipsor)
  - Apixaban (Eliquis)



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