

Medication Updates for 2019

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Learning Objectives

1. Name the new pharmaceutical agents available for clinical practice.
2. Explain the use of new pharmaceutical agents in clinical practice.
3. Summarize the benefits, risks, and alternatives of new pharmaceutical agents.

2018 Was the Busiest Year Ever

- FDA approved 59 new drugs and biologics which is up from a sluggish 23 in 2017 and a new record
- 33% were first in class
- 25% had breakthrough designations
- 2018 also stands out due to the projected cost increase of medications
 - Takes an average of \$2.6 B and >10 yrs to bring a drug to market
- Trend to create drugs that focus on specific cancers and rare diseases
- Leading those in primary care decreased access to prescribe newest therapies

Cardiovascular

AES Question



AES Question 1

At what level do the NCEP guidelines suggest starting a medication to target triglycerides specifically?

- A. 250mg/dl
- B. 500mg/dl
- C. 750mg/dl
- D. There is no definite level

Icosapent ethyl (Vascepa)

- Fish oil derived and highly purified form of EPA
- Indication:
 - Hypertriglyceridemia >500mg/dl per guidelines
- Dose:
 - 2g BID with meals
- Efficacy:
 - REDUCE-IT trial
 - 8,000 patients with ↑ risk CV risk already on a statin w/ TRG 135-499mg/dl
 - All at LDL goal
 - Over 4.9 years there was ~ 25% RRR in primary endpoints: CV death, nonfatal MI or CVA, coronary revascularization or unstable angina requiring hospitalization
- Safety:
 - Diarrhea, nausea, dyspepsia
- Cost:
 - ~\$300/month

Coagulation

Adexanet Alfa (Andexxa)

- First reversal agent by binding to the Xa inhibitor
- Indication:
 - Rivaroxaban (Xarelto) and Apixiban (Eliquis) reversal
 - Off label for Edoxaban (Savasya) and Betrixaban (Bevyxxa)
- Dose:
 - 400-800 mg IV bolus → 4-8 mg/min infusion (up to 120 minutes)
 - Dose depends which Xa inhibitor, doses given, and timing of last dose given
- Efficacy:
 - ANNEXA-4 trial: Decreased anti-Xa activity by an average of 89% after bolus → infusion
 - 4 hours post infusion: Decrease in 39% (rivaroxaban) and 30% (apixaban)
 - Effective hemostasis in 79% of patients
- Safety:
 - Thrombotic event in 18% of patients during 30 day follow up
 - Factor Xa can rebound after the end of infusion causing MI, ischemic events, embolic events, and sudden death
- Cost:
 - \$3,300/100mg dose

Dermatology

Glycopyrronium (Qbrexza)

- Topical anticholinergic that blocks activation of sweat glands
- Indication:
 - Treatment of primary axillary hyperhidrosis in pts \geq 9yo
- Dose:
 - One cloth for both underarms once daily
 - Does not take the place of deodorant
- Efficacy:
 - ATOMS-1 and ATOMS-2 trials
 - 53% and 66% reported reduced sweat production by roughly 1/2 vs 28% and 27% on placebo
- Safety:
 - Dry mouth, dilated pupils, HA, urinary retention, blurred vision
 - Avoid use with other anticholinergic medications
 - Potential for heat stroke?
- Cost:
 - \$580/month

Tildrakizumab-asmn (Ilumya)

- Second IL-23 antagonist on market
- Indication:
 - Treatment of moderate to severe plaque psoriasis
- Dose:
 - 100mg SC at weeks 0 and 4 and then every 12 weeks
 - Refrigerated and needs to sit out for 30 min prior to dose
- Efficacy:
 - Two efficacy and safety multinational trials
 - 64% and 61% had a 75% reduction in PASI score vs 9% with placebo
- Safety:
 - URIs, local site reactions, diarrhea
- Cost:
 - ~\$16,000/100mg dose vs. \$12,000/100mg dose of Tremfya

Endocrine

Semaglutide (Ozempic)

- Sixth GLP-1 analog
- Indication:
 - Type 2 DM
- Dose:
 - 0.25mg/weekly SC injection x 4 weeks then 0.5mg/week x 4 weeks then if needed max of 1mg/week
- Efficacy:
 - A1c reduction ~ 1.5% vs. exenatide (0.9%), sitagliptin (0.7%), and insulin glargine (0.9%)
 - Weight loss of 4-5kg
 - SUSTAIN 4 trial showed impact on CV endpoints
- Safety:
 - Nausea, vomiting, diarrhea, possible cholelithiasis
 - Do not use in those with retinopathy
- Cost:
 - \$583/dose at lower doses, but \$300/week if 1mg is maintenance dose

Ertuglifozon (Steglatro)

- Fourth SGLT2-inhibitor
- Indication:
 - Type 2 DM
- Dose:
 - 5mg/d with titration to 15mg/d
 - Caution if CrCl <60ml/min
 - CI with CrCl <30ml/min
- Efficacy:
 - A1c reduction <7% seen in 30-39% of patients (0.7-0.8% reduction)
- Safety:
 - Genital fungal infections, UTIs, HA
 - LE amputation at rate of 0.2-0.5% vs 0.1% in comparator group
- Cost:
 - \$320/month

Gastrointestinal Health

Prucalopride (Motegrity)

- Serotonin 5-HT₄ Receptor Agonist
- Indication:
 - Chronic idiopathic constipation
- Dose:
 - 1mg/day with max dose of 2mg/day
- Efficacy:
 - If no BM within 3-4 days add adjunctive laxative
 - Discontinue if not effective by 4 weeks
- Adverse Effects:
 - HA, nausea, diarrhea, abdominal pain
- Cost:
 - Not available prior to submission

Infectious Disease

Baloxavir marboxil (Xofluza)

- Oral antiviral
- Indication:
 - Management of influenza > 12yo and up if given within 48h of symptoms
- Dose:
 - 40-79kg use 40mg X 1 dose
 - ≥80kg use 80mg x 1 dose
- Efficacy:
 - Appears similar to a 5d course of oseltamivir
 - Possibly greater reduction in virus levels at 24 h & a shorter duration of virus detection
 - CAPSTONE -2 trial focused on high risk and showed shorter duration of symptoms vs. placebo
 - Data lacking for oseltamivir-resistant influenza or transmission within households/outbreaks
- Safety:
 - Diarrhea, Possible increased viral resistance
 - Avoid cations like Calcium- decreases absorption
 - No dosage adjustment in CKD
- Cost:
 - \$90/dose vs \$100 for 5 days oseltamivir

Rifamycin (Aemcolo)

- Oral antibacterial
- Indication:
 - Treatment of traveler's diarrhea caused by noninvasive *E. coli* without fever or blood in stool
- Dose:
 - Two tablets BID x 3 days
- Efficacy:
 - Approved based on evidence from two clinical trials N=1099
 - Conducted at 27 sites in India, Mexico, Guatemala, and Ecuador
 - Shorter duration of diarrhea (by approximately 22 hours) vs. placebo
- Safety:
 - Headache and constipation
- Cost:
 - Not available prior to submission, due on market first quarter of 2019

Omadacycline (Nuzyra)

- Antibiotic: Oral and IV Tetracycline Derivative
- Indication:
 - Treatment of CAP, Skin and Skin Structures (ABSSI)
- Dose:
 - Oral only ABSSI: 450mg X 2 days then 300mg daily X 7-14d
 - Must fast 4 h take dose with water then no food or drink x 2 h post dose
- Efficacy:
 - Activity against typical and atypical bacteria noninferior to Moxifloxacin
 - MSSA, MRSA, enterococcus, Strep, Klebsiella, E. cloacae
 - Noninferior to Linezolid with Gram (+) ABSSI
- Safety:
 - Nausea (2-22%), Vomiting, HTN, HA, ↑LFTs
 - Mortality Imbalance with CAP trial vs Moxifloxacin
- Cost:
 - ~\$7,000/14 days

Sarecycline (Seysara)

- Antibiotic: Oral Tetracycline Derivative
- Indication:
 - Moderate to severe acne vulgaris in children ≥ 9 yo
- Dose:
 - 33-54kg: 60mg/d
 - 55-84kg: 100mg/d
 - 85-136kg: 150mg/d
- Efficacy:
 - 3 clinical trials vs placebo
 - Reduction in acne over 12 week treatment period
- Safety:
 - Nausea, vomiting, diarrhea, teeth discoloration, slow bone growth
- Cost:
 - \$1030/month

Ozenoxacin (Xepi)

- Topical Quinolone antibacterial with activity against MSSA, MRSA, and *S. pyogenes*
- Indication:
 - Impetigo in infants ≥ 2 mos through adults
- Dose:
 - Apply BID x 5d
 - Up to 2% of BSA but do not exceed 100cm² in those <12 yo
 - >100cm² in those ≥ 12 yo
- Efficacy:
 - Two placebo controlled trials
 - Clinical success seen in 35% and 54% vs. 19% and 38% with placebo
 - No head to head trials but these cure rates suggest it is less effective than mupirocin or retapamulin (Altabax)
- Safety:
 - Well tolerated may see redness and irritation
- Cost:
 - 1% (per gram) \$11.88 vs. \$21 for retapamulin

Zoliflodacin

- Novel antibiotic
- Indication:
 - Management of Urogenital Gonorrhea
- Dose:
 - Could be 2-3g x 1 dose
- Efficacy:
 - Second of three clinical trials needed
 - 96% cure rate for urogenital and 100% for rectal infections
 - Underperformed for pharyngeal infections
 - Phase 3 trial starting in 2019
- Safety:
 - GI events reported
- Cost:
 - Not available prior to submission

Women's Health

Segesterone/Ethinyl Estradiol (Annovera)

- New progesterone and estrogen infused Vaginal Ring
- Indication:
 - Long term topical contraception
- Dose:
 - Segesterone 103mg/Ethinyl estradiol 17.4mg
 - Placed in vagina < 5d after cycle x 21 days then out for 7 days
 - End of dose free period re-insert SAME ring
 - Provides contraception for 13 cycles
 - Switching from other CHC just insert anytime during 28d cycle
- Efficacy:
 - 97.3% effective if used correctly
 - If out of vagina >7 days increased chance for pregnancy
- Safety:
 - BTB in first month, HA including migraine, N/V, infections
 - Increased VTE incidence in BMI > 29kg/m²
- Cost:
 - Not available prior to submission

Elagolix (Orilissa)

- GnRH antagonist – suppresses LH and FSH secretion leading to reduced estrogen secretion from ovaries
- Indication:
 - Endometriosis +/- dyspareunia
- Dose:
 - Endometriosis: 150mg/d x 24 months
 - With Dyspareunia: 200mg BID x 6 month
- Efficacy:
 - Noninferior to OCPs
 - Cannot use estrogen containing contraception since reduces efficacy of Elagolix
- Safety:
 - Bone loss, increased cholesterol, mood changes, menopausal symptoms
 - There is no symptom flare as seen with GnRH agonists
- Cost:
 - \$850/month

Etradiol Vaginal Inserts (Imvexxy)

- Topical estrogen replacement
- Indication:
 - Vulvar and vaginal atrophy associated with menopause
- Dose:
 - 4mcg daily x 2 weeks then taper to maintenance dose of 4mcg q 3-4 days
- Efficacy:
 - Lower dose option
 - Vaginal moisturizers are as effective as vaginal estrogens
- Safety:
 - HA, GI, local site reactions, hot flashes
- Cost:
 - \$378 for first two weeks \$210/month on maintenance

Neurology

Cannabidiol (Epidiolex)

- First Cannabidiol (CBD) oil approved by FDA
- Indication:
 - Children \geq 2 yo and adolescents
 - Severe seizures due to Lennox-Gastaut Syndrome or Dravet Syndrome
- Dose:
 - 2.5mg/kg BID increase in 1 week to 5mg/kg BID but quicker taper is outlined if needed
 - Maximum is 10mg/kg BID but side effect incidence was higher
- Efficacy:
 - 850 patients with LGS and Dravet syndrome refractory to 3-6 AEDs
 - LGS: 37-42% vs 17% seizure reduction
 - Dravet: 39% vs 13% seizure reduction
- Safety:
 - Sedation, lethargy, weakness, sleep disorder, ↓ appetite, GI
 - Liver toxicity: Baseline bili and LFTs then 1, 3, and 6 mos then periodically
- Cost:
 - \$14.82 per 100mg/ml solution

AES Question



AES Question 2

New biologic agents are more efficacious than traditional migraine prevention medications such as beta blockers.

- A. True
- B. False

Fremanezumab-vfrm (Ajovy)

- Calcitonin gene-related peptide (CGRP) receptor antagonist
- Indication:
 - Prevention of migraines
- Dose:
 - 225mg SC monthly or 675mg SC every 3 months
- Efficacy:
 - Prevents 1-2 more episodic migraines per month
 - ~50% reduction in frequency in half of the patients
 - Similar to other prophylactic meds
 - Can add to other oral prophylactic meds but no proof effect is additive
- Safety:
 - Injection site redness, antibody development
 - Theoretical concern for cardiac side effects but no long term data
- Cost:
 - \$460/month

Erenumab-aooe (Aimovig)

- Calcitonin gene-related peptide receptor antagonist
- Indication:
 - Prevention of migraines
- Dose:
 - 70mg SC monthly with max of 140mg SC monthly
- Efficacy:
 - Prevents 1-2 more episodic migraines per month
 - ~50% reduction in frequency in half of the patients
 - Similar to other prophylactic meds
 - Can add to other oral prophylactic meds but no proof effect is additive
- Safety:
 - Injection site redness, constipation, muscle cramps/spasms, antibody development
 - Theoretical concern for cardiac side effects but no long term data
- Cost:
 - ~\$600/month

Galcanezumab-gnlm (Emgality)

- Calcitonin gene-related peptide receptor antagonist
- Indication:
 - Prevention of migraines
- Dose:
 - 240mg SC loading dose then 120mg SC monthly
- Efficacy:
 - Prevents 1-2 more episodic migraines per month
 - ~50% reduction in frequency in half of the patients
 - Similar to other prophylactic meds
 - Can add to other oral prophylactic meds but no proof effect is additive
- Safety:
 - Injection site redness, antibody development
 - Theoretical concern for cardiac side effects but no long term data
- Cost:
 - ~\$600/month
 - Drug maker is offering no cost for 1 year to patients with commercial insurance

Opioid Misuse

AES Question



AES Question 3

Which of following is correct about lofexidine (Lucemyra)?

- A. It precipitates withdrawal symptoms in those dependent on opioids
- B. It is not absorbed from GI tract
- C. It is administered 4 times a day
- D. It is similar to a beta blocker

Lofexidine (Lucemyra)

- Central α -2 adrenergic agonist
- Indication:
 - Mitigation of opioid withdrawal symptom to facilitate abrupt opioid discontinuation
- Dose:
 - 0.56mg as 0.18mg tablet X 3 tablets (max 0.72mg) q 5-6 hours x up to 14d
 - Must taper off: 1 tab per dose q 1-2 days
- Efficacy:
 - Two placebo controlled trials: Study completion was 41% vs 29% and 49% vs 33%
 - SOWS-Gossop score used to quantify withdrawal symptoms
 - Both trials showed lower withdrawal scores vs placebo
- Safety:
 - Hypotension, bradycardia, dizziness, sedation, dry mouth
 - Prolongs QT- caution with methadone
 - Must separate oral naltrexone dose by 2 hours
- Cost:
 - ~\$3500/14 day course

Pain Management

ZTLido (Lidocaine)

- Topical anesthetic
- Indication:
 - Postherpetic Neuralgia
- Dose:
 - 1.8% per patch, can apply up to 3 patches
 - 12h on then 12 h off
 - Equivalent to Lidoderm 5% patch
- Efficacy:
 - Noninferior to Lidoderm but is not AB rated
 - Supposedly adheres to skin better than lidoderm
- Safety:
 - Flushing, confusion, HA, local skin reactions
- Cost:
 - \$9/ patch vs \$7/patch for lidoderm

Benzhydrocodone/APAP (Apadaz)

- Opioid analgesic prodrug
- Indication:
 - Pain management after failure with non-opioid options
- Dose:
 - Benzhydrocodone 6.12mg/APAP 325mg: 1-2 Tabs q 4-6 h prn
 - Equivalent to hydrocodone 7.5mg/APAP 325mg
 - C-II
- Efficacy:
 - Same as all C-II opioid products
- Safety:
 - Itching, constipation, sedation
 - Same risk of addiction, abuse, and misuse
- Cost:
 - Not available prior to submission

Respiratory

Revefenacin (Yupelri)

- First once a day nebulized LAMA
- Indication:
 - Maintenance therapy for COPD
- Dose:
 - 175mcg (1 unit dose vial) daily
- Efficacy:
 - Two Phase 3 clinical trials for approval
 - Statistically and clinically meaningful improvements in FEV1 after 12 weeks of treatment vs placebo
- Safety:
 - Cough, URI, HA, and back pain
- Cost:
 - ~\$360/month vs. \$200 for Spiriva Respimat

Biologics

Biosimilar Expansion in 2018

- Highly similar to “parent” biologics in purity, physiochemical characteristics, potency, and safety
- Examples of some approved in 2018:
 - *Nivestym and Zarxio for filgrastim (Neupogen)*
 - *Fulphila for pegfilgrastim (Neulasta)*
 - *Inflectra and Renflexis for infliximab (Remicade)*
- Substitution or Interchange of products
 - BPCI Act of 2009 gives 1 yr of exclusive marketing rights to the first biosimilar approved
 - Biosimilars are NOT generics – indications vary greatly
 - There are no interchangeable biologics yet!!
- Naming is based on a random 4 letter suffix devoid of meaning
 - Allows differentiation of biosimilars with suffix evening playing field
 - Common core names group them within EMR

Game Changers in the Market

Changes in 2018

Did not make the show:

- Baricitinib (Olmiant) – oral RA
- Epoetin alpha-epdx – 1st Biosimilar for Epogen
- SUFentanil (Dsuvia) – POTENT pain reliever
- Methylphenidate (Jornay PM) – Early AM control in ADHD

Went Generic 2018-2019:

- Tadalafil (Cialis)
- Memantine (Namenda XR)
- Sumatriptan/naproxen (Treximet)
- Exenatide (Byetta)
- Vardenafil (Levitra)
- Epinephrine (Epi-Pen)
- Fluticasone/Salmeterol (Advair diskus)
- Solifenacin (Vesicare) May 2019
- Pregabalin (Lyrica) July 2019

Best Practice Recommendations

- Evolution of industry showing research in areas that will yield high profits ie biologics, DM care, autoimmune diseases, precision medicine
- Primary Care physicians on average usually wait 12-18 months to use a new product.
- Awareness is crucial to determine when and in what type of patient a new product may work
- Quick and easy information is needed for the current pace of life
- Choose three resources that fit your needs
 - Prescribers Letter
 - Lexicomp App
 - Medscape
 - AAFP daily emails
 - <https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm>
 - <https://www.centerwatch.com/drug-information/fda-approved-drugs/>
 - Others?!

Answers

1. B
2. B
3. C



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