

Drug Updates for 2016

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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.

2016 Was Not A Busy Year

- FDA only approved 22 new drugs and biologics which is down from 45 last year
- The 11 year average is 25 novel new drugs per year
- Many others were approved but they were “re-issues” of existing drug entities or alterations in delivery systems
- Reasons cited:
 - 5 applications were processed earlier and made 2015
 - Fewer applications submitted by manufacturers
 - FDA issued more rejections due to manufacturing concerns
 - Increase in CRLs- meaning drug not accepted with current information

Endocrine



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Extended Action Orals

- Invokamet XR (Canaglifozin + Metformin)
 - Starting dose is 50-500 and titrate to 150-1000
 - Maintenance dose is 2 tabs daily
 - Converting from 2 drugs to combo is a 1:1 dosing
 - If on one drug and not the other, start at lower dose for new drug and do 1:1 conversion for the other
 - Same side effects, precautions, and warnings for each class
 - Cost \$470/month
- Jentaduetto XR (Linagliptin + Metformin)
 - Starting dose 2.5-1000 and titrate to 5-2000mg
 - Converting from two drugs to one is 1:1 dosing
 - If on one drug and not the other, start at lower dose for new drug and 1:1 for the conversion of the other
 - Same side effects, precautions, and warnings for each class
 - Cost \$450/month

Insulin Glargine (Basaglar)

- Third glargine on market but not generic
- Indication:
 - Management of DM1 and DM2
- Dose:
 - Starting LA insulin use 10 units/day
 - Titrate to 30-50% of total daily insulin requirement
 - Converting from Lantus is a 1:1 equivalent
 - Converting from Toujeo reduce dose by 20%
- Efficacy:
 - No difference between insulins
- Adverse Effects:
 - Hypoglycemia, weight gain
- Cost:
 - Only available as Kwikpen
 - 3ml cost is \$76 vs \$90 for Lantus vs \$134 for Toujeo
 - Must write specifically for this insulin, not a therapeutic interchange

Lixisenatide (Adlyxin)

- Sixth GLP-1 agonist
- Indication:
 - Type 2 Diabetes
- Dose:
 - Initial 10mcg SC daily x 14 days then increase to 20mcg daily for maintenance
 - Administer 1 hour prior to first meal of day
 - CKD 5 do not use
- Efficacy:
 - Average about a 1% reduction in A1c vs. Liraglutide at 1.5%
 - Average short term weight loss is 2kg vs 2.5kg with Liraglutide
- Adverse Effects:
 - Nausea 25%
 - Pancreatitis, Gastroparesis, AKI
- Cost:
 - Multi dose pens with 14 doses per pen
 - Cost \$600 for 20mcg dose
 - Once opened can be stored at room temperature

Insulin Glargine/Lixisenatide (Soliqua)

- First combination long acting insulin with GLP-1
- Indication:
 - Type 2 DM but on <60u of insulin or on metformin + GLP-1
 - May see this added to metformin to minimize costs, reduce injections, and increase efficacy
- Dose:
 - Uncontrolled on <30u of basal insulin: Initiate at 15 units
 - Uncontrolled on 30-60 units of basal insulin: Initiate at 30 units
 - Titrate 2-4 units weekly to max of 60 units insulin and 20mcg lixisenatide
- Efficacy:
 - A1c ↓0.5% more than using insulin glargine alone
 - Weight loss of 1.4kg
- Adverse Effects:
 - Nausea 10%, all other side effects same for each class
- Cost:
 - Multi-dose pens 3ml (100 units and 33mcg/ml) with cost of \$600-700
 - Each pen delivers 15-60 units of insulin per injection
 - If pen is not depleted by 14 days has to be discarded

Insulin Degludec/Liraglutide (Xultophy)

- Combination long acting insulin and GLP-1 on market in 2017
- Indication:
 - Type 2 DM
 - Addition to metformin?
- Dose:
 - Initiate 16units of insulin with or without food
 - Titrate 2 units every 3-4 days to max of 50 units insulin and 1.8 mcg liraglutide
- Efficacy:
 - A1c ↓1% vs insulin degludec alone
 - Weight loss 2kg
- Adverse effects:
 - Nausea is 10%, all other side effects same for each class
- Cost:
 - Multi dose pens (100units and 3.6mcg/ml) with max cost of \$950
 - Each pen delivers 10-50 units
 - Discard after 21 days

Cardiovascular



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Nebivolol/Valsartan (Byvalson)

- Combination Beta Blocker and ARB
- Indication:
 - Hypertension
 - Consider for post MI requiring both classes
- Dose:
 - Nebivolol 5mg/Valsartan 80mg/day
 - Adjust with CrCl<30ml/min
- Efficacy:
 - Combination product for combined efficacy (Rule of 10)
 - Higher dose of 10-160mg did not decrease BP much further
 - No data that outperforms other combinations
- Adverse Effects:
 - BB: causes bradycardia, weight gain, fatigue, ED
 - ARB: causes angioedema, SCr increase
- Cost:
 - 5-80mg tablet only
 - Cost \$131/month

Enalapril (Epaned) and Lisinopril (Qbrelis)

- ACE-I Oral solution
- Indications:
 - LVH, HFrEF, HTN, AMI
- Dose:
 - Enalapril
 - LVH has dose titration ending with 10mg BID
 - HFrEF 2.5mg BID to max of 20mg BID
 - HTN 2.5mg BID to max of 20mg BID
 - Lisinopril
 - AMI has dose titration ending with 10mg/d
 - HFrEF 2.5-5mg/d to max of 40mg/d
 - HTN 10mg/d to max of 40mg/d
- Efficacy:
 - Significant impact proven for this class with all indications
- Adverse Effects:
 - Cough, angioedema, increase K and SCr, hypotension, dizziness
- Cost:
 - 1mg/ml Solution (150ml) for both
 - Cost \$590.00 for both

At what age does the USPTF recommend starting aspirin therapy as primary prevention if the patient's ASCVD score is $\geq 10\%$?

- A. 40
- B. 50
- C. 60
- D. 65

Aspirin/Omeprazole (Yosprala)

- Combination antiplatelet and PPI
- Indication:
 - Secondary prevention of MI and CVA/TIA
 - Reduction in risk of ASA induced ulcers in susceptible patients
 - NOT for use as initial ASA therapy for ACS, MI, or PTCA
- Dose:
 - 81mg ASA and 40mg omeprazole
 - 325mg ASA and 40mg omeprazole
- Efficacy:
 - PPI efficacy is known, however there is no EBM that PPI ↓ the risk of GI bleed due to ASA
 - Efficacy for ASA 81mg is universally understood but at times 325mg is needed
- Adverse effects:
 - PPI: increased fx risk, possible C diff increase, B12 deficiency
 - ASA: GI irritation, bleeding, bruising
- Cost:
 - Cost \$180/month for both dosages

Infectious Disease



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Bezlotoxumab (Zinplava)

- Monoclonal antibody that binds to *C. difficile* toxin B to neutralize the infection
- Indication:
 - Reduce the recurrence of *C. difficile* infection
 - Used in conjunction with antibacterial treatment
- Dose:
 - Single dose of 10mg/kg as IV given over 1 hour
- Efficacy:
 - Dosed with antibacterials at any point in therapy
 - Recurrence was lower vs placebo in high risk pts through 12 weeks post-infusion
- Adverse effects:
 - >4% reported nausea, fevers, headaches, other infusion reactions resolving with 24h
 - Caution in HFrEF
- Cost:
 - 1000mg/40ml infusion
 - Cost \$4560 x 1 dose

Tenofovir Alafenamide (Vemlidy)

- Hepatitis B nucleoside reverse transcriptase inhibitor
- Indication:
 - Treatment of chronic HBV infection in adults with compensated liver disease
- Dose:
 - 25mg daily with food
- Efficacy:
 - Noninferior to Tenofovir Disoproxil Fumarate in reducing viral load, normalizing LFTs, and seroconversion
 - Cannot be used as monotherapy if co-infected with HIV
- Adverse Effects:
 - Lactic acidosis, severe hepatomegaly, and possible AKI
 - Acute exacerbation of hepatitis after D/C of med
 - Risk of developing HIV resistance if co-infected
- Cost:
 - Cost \$1200/month
 - Patent ending for other salt form of Tenofovir

Which of the following vaccinations should be recommended specifically for patients with HCV?

- A. Meningococcal
- B. Varicella
- C. Yellow Fever
- D. Hepatitis A and B

Sofosbuvir/Velpatasvir (Epclusa)

- Fixed dose combination of NS5B RNA polymerase inhibitor + NS5A replication complex inhibitor
- Indication:
 - Chronic HCV genotypes 1-6 without cirrhosis or with compensated liver
 - Or in combination with ribavirin in those with decompensated liver
- Dose:
 - 1 fixed dose tablet daily x 12 weeks +/- ribavirin (24 weeks if cannot use ribavirin with decompensated liver)
- Efficacy:
 - ASTRAL-1 trial showed sustained virologic response (SVR) ~99% in all genotypes
- Adverse Effects:
 - Fatigue, HA, GI, insomnia
- Cost:
 - Month supply cost \$30,000 x 3 months= \$90,000

Elbasvir/Grazoprevir (Zepatier)

- Fixed dose combination of NS5A replication complex inhibitor plus NS3/4A protease inhibitor
- Indication:
 - Treatment of chronic HCV genotypes 1 or 4 +/- ribavirin based on previous therapies
 - Length of therapy ranges from 12-16 weeks based on genotype and previous therapies
 - Can be used if co-infected with HIV
- Dose:
 - 1 fixed dose tablet 12-16 weeks
- Efficacy:
 - C-EDGE trial showed genotype 1 SVR ~ 92-99%
- Adverse Effects:
 - Fatigue, HA, GI, insomnia, asthenia
- Dosage Form:
 - Month supply \$22,000 x 3-4 months = \$66,000-88,000

HPV 9 Vaccine (Gardasil)

- Additional guidance on use of HPV-9 was issued in 2016
- Indication updated:
 - ACIP recommendation: Women ≥ 9 yo and ≤ 26 yo; **Men ≥ 9 yo and ≤ 21 yo**
 - **Men ≤ 26 yo if considered higher risk**
- Dosing:
 - **Remains 3 shot series HOWEVER now 9-14yo can have 2 dose series**
 - Can complete the HPV-4 series with HPV-9
 - No recommendation to re-vaccinate if already had series
- Efficacy:
 - Added strains are 31, 33, 45, 52, 58
 - Offers additional coverage that accounts for ~14% of cancers in women and 4% for men
 - Do NOT have to revaccinate but in clinical trial this did show antibody titers against the 5 additional HPV types
- Cost:
 - Per CDC and VFC \$380 for series

Controlled Substances



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Oxycodone/Naltrexone (Troxyca ER)

- Combination narcotic with abuse deterrent
- Indication:
 - **Scheduled** dosing for relief of chronic pain
- Dose:
 - 10mg/1.2mg up to 80mg/9.6mg
 - Based on past opioid use and level of patient tolerance
- Efficacy:
 - Naltrexone is released if pellets are crushed and acts like the IR form
 - “Drug Liking” scale used in clinical trials showed ~90% would not take this drug via intranasal or IV route
 - Deter seekers from snorting or using IV
 - Oral formulation works and compares to long acting oxycodone
- Adverse Effects:
 - Talc in the formulation - if used IV will see skin necrosis, infection, and possible endocarditis
- Cost:
 - Capsule with pellets
 - Large range of dosages
 - Cost unavailable at time of submission

Buprenorphine (Probuphine)

- Subdermal implant for maintenance buprenorphine dosing
- Indication:
 - Maintenance treatment if stable on low to moderate doses of buccal buprenorphine (<8mg/d) \geq 3 months and require at least 6 months more of therapy
 - Requires special DEA certification and live training program to prescribe
- Dose:
 - Insert 4 implants sub-dermally inner side of upper arm with 1 week F/U after insertion
 - Lasts 6 months
- Efficacy:
 - Noninferior to buccal buprenorphine in a specific population reflected within indication
- Adverse Effects:
 - HA, itching, redness, bleeding
- Cost:
 - Kit has 4 sterile implants each with 80mg of drug and one applicator
 - Implant is 26mm in length and 2.5mm in diameter
 - Cost \$6000 for kit

Gastrointestinal Health



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Which side effect caused by opioids does not lessen as tolerance increases?

- A. Respiratory depression
- B. Itching
- C. Constipation
- D. Somnolence

Methylnaltrexone (Relistor)

- Oral formulation of selective opioid antagonist at peripheral mu receptors in GI tract, does not cross the BBB
- Indication:
 - Opioid induced constipation in chronic non-cancer pain
 - D/C all other laxatives before starting
 - Can restart laxatives if no results in 3 days
- Dose:
 - Oral is 450mg daily taken on empty stomach with water 30 min before breakfast
 - Dose adjust for CrCl < 60ml/min to 150mg daily
- Efficacy:
 - 13% more patients had 1 or more BM per week vs placebo in a 4 week trial of 400 patients
- Adverse Effects:
 - Withdrawal like symptoms: abdominal pain, flatulence, N/V, dz, sweating, anxiety, chills
 - Possible increase in perforation in those with h/o PUD, GI cancers, or diverticular disease
- Cost:
 - 150mg tablets
 - Costs \$1800/month

Women's Health



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Prasterone (Intrarosa)

- Vaginal insert of inactive steroid converted to active androgen and/or estrogen
- Indication:
 - Treatment of moderate to severe dyspareunia
- Dosing:
 - Intravaginal application of 6.5mg at bedtime
- Efficacy:
 - Superior to placebo in reducing pain
 - Limited clinical trials, both were 12 weeks
- Adverse Effects:
 - Vaginal discharge
 - Abnormal PAP results at 52 weeks
- Cost:
 - Bullet shaped inserts (28 in a box with 28 applicators)
 - Cost unknown since not on market yet, approved November 2016

Dermatology



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Crisaborole (Eucrisa)

- PDE-4 inhibitor
- Indication:
 - Mild to moderate atopic dermatitis \geq 2yo
- Dose:
 - Thin layer applied BID
- Efficacy:
 - Two clinical trials lasting 28d
 - First trial 32.8% achieved success vs 25.4%
 - Second trial 31.4% achieved success vs 18%
 - Third line therapy after failure of steroids or when steroids cannot be used
 - No CA risk as seen in case reports with Elidel and Protopic
- Adverse Effects:
 - Application site pain
- Cost:
 - 60g tube cost \$700

Biologics



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Biosimilars Are On The Market

- Highly similar to FDA approved biologics in physiochemical characteristics, purity, potency, efficacy and safety
- Three approved in 2016:
 - ***Adalimumab-atto (Amjevita) – Similar to Humira***
 - *Crohn's, UC, RA, ankylosing spondylitis, psoriasis*
 - ***Etanercept-szzs (Erelzi) – Similar to Enbrel***
 - *RA, polyarticular JIA, ankylosing spondylitis, psoriasis*
 - ***Infliximab-dyyb (Inflectra) – Similar to Remicade***
 - *Crohn's, RA, ankylosing spondylitis, psoriasis*
- Substitution or Interchange of products
 - BPCI Act of 2009 gives 1 yr of exclusive marketing rights to the first biosimilar approved as being interchangeable with reference biologic
 - Can be done without prescriber input but watch indications they vary
- Naming is based on a random 4 letter suffix devoid of meaning
 - Allows differentiation of biosimilars
 - Common core names group them within EMR
 - Suffix for all products evens playing field with inferiority perceptions

Did Not Make the Show



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Approved in 2016-2017

- Cinquair – IL-5 blocker for asthma
- Talz – IL 17A blocker for psoriasis
- Bevespi – LAAC/LABA combo
- Bonjesta – ER nausea in pregnancy
- Zinbryta – IL 2 Blocker for MS
- Vermox – chewable for ringworm
- Xeljanz XR – extended release
- Zembrace – migraine injectable
- Belviq XR – Weight loss
- Kyleena – Progesterone IUD

Best Practice Recommendations

- Evolution of industry showing research in areas that will yield high profits ie biologics, DM care, autoimmune diseases
- 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
 - Others?!



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