NEW DRUG UPDATE 2016

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Accreditation

• New Drug Update 2016 is accredited for 1.5 contact hours
  – Pharmacists  ACPE 0154-0000-16-010-L01-P
  – Technicians  ACPE 0154-0000-16-010-L01-T
  – Bryson Duhon & Laurajo Ryan have not disclosed any financial or conflicts of interest in relation to this program
Presentation Objectives

1. Discuss the basic pharmacology of the new drugs presented and how the pharmacologic actions relate to both therapeutic and adverse effects.

2. Discuss clinically significant adverse effects and drug interactions, and the appropriate dosing and monitoring of the new drugs presented.

3. Discuss the therapeutic role of the new drugs presented as compared to agents already marketed.

- Crestor – $6.4 billion annual revenue
- Benicar – $2.6 billion annual revenue
- Zetia – $2.6 billion annual revenue
- Cubicin – $1.5 billion annual revenue
- Seroquel XR – $1.2 billion annual revenue
- Aciphex Sprinkle – $1.1 billion annual revenue
- Norvir – $1.0 billion annual revenue
- Kaletra – $1.0 billion annual revenue
- Epzicom – $1.0 billion revenue

http://medcitynews.com/2016/01/drugs-off-patent/
FDA Drug Approvals in 2015/2016

• 2015
  – 45 new drug approvals (most since 1950)
  – 16 with novel MOA (36%)
  – Almost ½ used for rare diseases
  – Expedited review granted to 60% of new drugs

• 2016
  – 29 drugs approved so far

http://cen.acs.org/articles/94/i5/Year-New-Drugs.html
IDARUCIZUMAB
(PRAXIBIND®-BOEHRINGER-INGELHEIM)
Idarucizumab

• Dabigatran reversal agent
  – Life-threatening or uncontrolled bleeding
  – Emergent/urgent procedure
Idarucizumab

• Humanized monoclonal antibody fragment (Fab)
  – Binds specifically to dabigatran & dabigatran metabolites
    • 350X affinity for dabigatran vs. thrombin
  – Reverses anticoagulant effects
    • Onset in minutes
    • Hemostasis ~11 ½ hours
  – Does not interfere with clotting proteins directly

JACC 2016;67:1654
Idarucizumab

• Dosing
  – 5g IV
    • Push or infusion
    • 2X 2.5g (50mL)
      – ≤ 15 minutes apart
  – Continued or repeat bleeding
    • Data on 2\textsuperscript{nd} dose limited
Idarucizumab

- Adverse effects
  - Headache
  - Hypokalemia
  - Delirium
  - Potential immune reaction
  - Thrombotic risk
    - No increase over baseline
Idarucizumab

• Some subjects in RE-VERSE AD™ trial
  – Re-elevation of bleed risk
  – Redistribution of dabigatran from tissues to plasma
CEFTAZIDIME/AVIBACTAM
(AVYCAZ®-ALLERGAN/ASTRAZENECA)
Ceftazidime/Avibactam

• 50,000 Foot View
  – Antibiotic with novel beta lactamase inhibitor used for “Armageddon” gram – negative pathogens

• Drug Class
  – Cephalosporin class antibiotic

• FDA Indications
  – Complicated intra – abdominal infections
    • In combination w/ metronidazole
  – Complicated urinary tract infections
    • In combination w/ metronidazole
Ceftazidime/Ahibactam

• MOA
  – Ceftazidime
    • 3rd generation cephalosporin on market since 1980s
    • Cell wall inhibitor (binds PBPs)
    • Activity vs. Pseudomonas spp.
  – Ahibactam
    • Beta lactamase inhibitor
    • Active vs. AmpC, ESBL, KPC
    • Not active vs. metallo – beta lactamases
Ceftazidime/Avibactam

- Dosing (IV only)
  - 2.5 g every 8 hours in combination with metronidazole
  - For 5 – 14 days in cIAI
  - For 7 – 14 days in cUTI
- Contains 2g of ceftazidime and 0.5g of avibactam
- Dosing based on the sum of ingredients (e.g. 2.5 g)
- Requires renal dose adjustment w/ CrCl < 50 mL/ min
- Administer after dialysis
- Administer over two hours
Ceftazidime/Avibactam

• Clinical Evidence
  – cIAI (Lucasti JAC 2013; Mazuski CID 2016)
    • Ceftaz/avi + metro non inferior to meropenem
  – cUTI (Vazquez Curr Med Res Opin 2012)
    • Ceftaz/avi + metro non inferior to imipenem/cilastatin

• Safety Data
  – Nonspecific GI symptoms / headache
  – One case of increased LFTs
  – Well tolerated
Ceftazidime/Avibactam

• Drug Interactions
  – May increase effect of VKAs
  – Levels decreased by probenecid

• Warnings and Precautions
  – Neurotoxicity w/ high dose (β lactam, duh)

• Pregnancy Category B / excreted in breast milk

• Contraindications
  – Hypersensitivity to cephalosporins
Ceftazidime/Avibactam

• Market Niche
  – Serious gram negative infections
  – Containing KPC beta lactamases
  – Sparing toxic alternatives (i.e. colistin)
  – Indicated in cIAI and cUTI, but likely to be used off label in dire situations

• Pricing: $1,000 / day AWP
SUGAMMADEX
(BRIDION®-MERCK)
Sugammadex

• Antidote
  – Selective reversal of aminosteroidal non-depolarizing neuromuscular blockers
    • Rocuronium > vecuronium >> pancuronium

• Mechanism of action
  – Binds rocuronium 1:1
    • Decreases free rocuronium
      – Forms plasma gradient
    • Bound rocuronium diffuses from neuromuscular junction
      – Newly free rocuronium binds to sugammadex
    • Water-soluble complex
      – Excreted unchanged in the urine
Sugammadex

• Dosing
  – Routine reversal of neuromuscular blockade
    • IV as single dose based on actual body weight
      – Deep blockade = 4mg/kg
      – Moderate blockade = 2mg/kg
  – Immediate reversal of neuromuscular blockade
    • IV 16mg/kg
      – Within 3 minutes of 1.2mg/kg of rocuronium dose
  – Wait times for re-administration vary
    • If immediate neuromuscular blockade required after sugammadex
      – Can use non-steroidal agent
Sugammadex

• Drug interactions
  – Displacement by steroid-like structures
  – Toremifene
  – Fusidic acid
  – Progesterones?

• Monitor for recurrence of neuromuscular blockade
PATIROMER
(VELTASSA®-RELYPSA)
Patiromer

• Antidote for hyperkalemia
  – For chronic administration is patients who require RAAS inhibitors
  – Not for emergent use

• Mechanism
  – Non-absorbable cation-exchange polymer
    • Calcium/sorbitol
Patiromer

• Dosing
  – 8.4g oral daily
    • Mix powder with water; drink immediately
    • Take with food
    • Adjust ≥ weekly; max dose 25.2g per day

• Drug interactions
  – Boxed warning
    • Binds oral drugs—separate doses by 6 hours before/after

• Adverse effects
  – Hypomagnesemia
  – GI
    • May cause constipation or diarrhea
    • Ineffective in severe constipation
ROLAPITANT
(VARUBI®-TESARO)
Rolapitant

• Anti-emetic
  – Indicated for prevention of delayed chemotherapy-induced nausea & vomiting (CINV)

• Mechanism of action
  – Substance P/neurokinin 1 (NK₁) receptor blocker
    • Substance P stimulates chemoreceptor trigger zone causing nausea/vomiting
Rolapitant

- Highly emetogenic therapy
  - 180mg 1-2 hours prior to therapy on day 1 only
    - Give with dexamethasone & 5-HT₃ regimen
    - Do not give more frequently than Q2 weeks

- Moderately emetogenic therapy
  - 180mg 1-2 hours prior to therapy on day 1 only
    - Do not give more frequently than Q2 weeks

- t½ ~7 days
- Metabolized via CYP3A4 to active metabolites
ISAVUCONAZOLE
CRESEMBA®-ASTELLAS
Isavuconazole

• 50,000 Foot View
  – Antifungal w/ activity against *Aspergillus* and *Mucormycoses* spp.

• Drug Class
  – Azole antifungal

• FDA Indications
  – Invasive Aspergillosis
  – Invasive Mucormycosis
Isavuconazole

• MOA
  – Inhibits CYP 450 – dependent 14α – lanosterol
  – Essential for fungal cell membrane formation
  – Active against yeasts, molds

• Administered as prodrug
  – 186 mg isavuconazonium sulfate = 100 mg isavuconazole

• Dosing
  – Loading Dose: 372 mg q 8 hours x 6 doses
  – Maintenance Dose: 200 mg once daily
Isavuconazole

• Available IV and PO; 98% bioavailability
• Very long half – life = > 4 days
• Metabolized via CYP 3A4
  – Not recommended in advanced liver disease
• Eliminated via feces
  – No need for renal dose adjustment
  – Not good for UTI treatment
Isavuconazole

• Clinical Evidence
  – SECURE: non – inferior to voriconazole for aspergillus
  – Preliminary data vs. *Mucormycoses* indicate similar mortality to historical data (35%)
  – Limited data against *Fusarium / Endemic molds*

• Safety Data
  – Nonspecific GI symptoms
  – No visual disturbances like voriconazole
  – Liver enzyme elevations (it’s an azole)
  – Shortens QTc
  – Infusion reactions in a few patients → use filter
Isavuconazole

• Drug Interactions
  – CYP 3A4 → rifampin, CBZ, immunosuppressants

• Warnings and Precautions
  – Hepatic effects (10x LFTs in 1.2%)
  – Infusion related reactions

• Pregnancy Category C / excreted in breast milk
  – Higher perinatal mortality in rats w/ half maintenance dose

• Contraindications
  – Use of strong 3A4 inhibitors/inducers
  – Familial short QTc syndrome
Isavuconazole

• Market Niche
  – Alternative to voriconazole for Aspergillosis
    • Better bioavailability
    • Better side effect profile
  – Alternative to posaconazole / another option against Mucormycoses
    • Better bioavailability

• Pricing
  – IV: One dose = $285
  – PO One dose = $168
INSULIN DEGLUDEC
TRESIBA® — NOVO NORDISK
Insulin Degludec

• 50,000 Foot View
  – Ultra – long acting basal insulin with promises to reduce hypoglycemia

• FDA Indications
  – Improved glucose control in Type 1 and Type 2 diabetes mellitus
Insulin Degludec

• Dosing
  – T1DM
    • Insulin – naïve: 1/3 to 1/2 of total daily insulin dose (usually 0.2 – 0.4 units/kg) given once daily
    • Insulin – experienced: Same dose at total daily basal dose
  – T2DM
    • Insulin – naïve: 10 units once daily
    • Insulin – experienced: Same dose at total daily basal dose
  – Ensure 8 hours between consecutive doses
Insulin Degludec

• Pharmacology
  – Uses phenol in formulation to form soluble dihexamers
  – Once injected subcutaneously, phenol disperses, and self–associates into larger multihexamers
  – Individual insulin molecules gradually dissociate as monomers

• Kinetics
  – Steady absorption
  – Zero–order kinetics
  – Onset = 30 – 90 minutes
  – Half–life = 25 hours
  – Duration of action > 42 hours
Insulin Degludec

• Differences from detemir and glargine
  – Less variability in blood glucose lowering from injection to injection
  – Ability to co-formulate with bolus insulins
    • Glargine forms precipitate
    • Detemir lowers effect of bolus insulin
    • Degludec in combo w/ aspart in development
  – Increased flexibility in dosing
    • Changes in injection time w/ degludec do not adversely effect glucose control
  – Stability in hepatic/renal disease
# Insulin Degludec

## BEGIN Basal – Bolus Type 1

<table>
<thead>
<tr>
<th></th>
<th>Degludec</th>
<th>Glargine</th>
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<tbody>
<tr>
<td><strong>A1c Reduction</strong></td>
<td>0.4%</td>
<td>0.39%</td>
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<tr>
<td><strong>Nocturnal Hypoglycemia</strong></td>
<td>3.9%</td>
<td>5.2%</td>
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## BEGIN Basal – Bolus Type 2

<table>
<thead>
<tr>
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<th>Degludec</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1c Reduction</strong></td>
<td>1.1%</td>
<td>1.18%</td>
</tr>
<tr>
<td><strong>Overall Hypoglycemia</strong></td>
<td>11%</td>
<td>13.6%</td>
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</table>

Lancet 2012;379(9825): 1489-97
Lancet 2012;379(9825): 1498-1507
Insulin Degludec

• Warnings and Precautions
  – Hypoglycemia / hypokalemia
  – Not for use in DKA

• Pregnancy Category C
  – Not studied in pregnant woman / animal studies revealed adverse events due to maternal hypoglycemia

• Excreted in breast milk

• Optimal transition dosing from other long – acting insulins yet to be elucidated

• Storage: Stable for 8 weeks at room temperature
Insulin Degludec

• Market Niche
  – Already co-formulated with insulin aspart
    • IDegAsp $\rightarrow$ Ryzodeg 70/30®
  – The Future
    • IDegLira $\rightarrow$ liraglutide/degludec co-formulation

• Pricing
  – 100 units/mL (3 mL) = $100
  – 200 units/mL (3 mL) = $213
SELEXIPAG
(UPTRAVI® – ACTELION)
Selexipag

• 50,000 Foot View
  – New PAH drug for early stage disease (WHO II/III)
• MOA
  – Prostacyclin IP receptor agonist → relaxed smooth muscle
  – Less GI effects than other PAH drugs
• Dosing
  – Started at 200 mcg twice daily
  – Titrated weekly up to 1600 mcg twice daily
  – If dose missed for >3 days, restart at lower dose
• Avoid gemfibrozil in combination
• One tablet = $155
PIMAVANSERIN
(NUPLAZID® – ACADIA)
Pimavanserin

• 50,000 Foot View
  – Non dopamine atypical anti-psychotic for Parkinson’s psychosis

• MOA
  – Inverse agonist of serotonin 5-HT2A
  – Exciting target for psychosis of different diseases

• Dosing
  – 34 mg Q Day (1/2 dose w/ Strong 3A4 inhibitors)

• Can prolong QTc interval
# Antipsychotic Receptor Activity

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Pimavanserin</th>
<th>Haloperidol</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
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<tbody>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>0.4</td>
<td>50</td>
<td>7</td>
<td>2.5</td>
<td>250</td>
<td>0.2</td>
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<tr>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>nr</td>
<td>nr</td>
<td>40</td>
<td>80</td>
<td>1100</td>
<td>12</td>
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<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
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<td>nr</td>
<td>40</td>
<td>80</td>
<td>nr</td>
<td>100</td>
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<td>nr</td>
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<td>5</td>
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<td>60</td>
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<td>M2</td>
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<td>M3</td>
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<td>40</td>
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<td>D1</td>
<td>nr</td>
<td>100</td>
<td>nr</td>
<td>100</td>
<td>-</td>
<td>60</td>
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<td>30</td>
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<td>Alpha 1A</td>
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<td>8</td>
<td>100</td>
<td>nr</td>
<td>3</td>
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<tr>
<td>Alpha 1D</td>
<td>-</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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<td>50</td>
</tr>
<tr>
<td>Alpha 2A</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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<td>nr</td>
<td>50</td>
<td>nr</td>
<td>nr</td>
<td>50</td>
</tr>
<tr>
<td>Alpha 2C</td>
<td>nr</td>
<td>50</td>
<td>40</td>
<td>nr</td>
<td>nr</td>
<td>13</td>
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*Ki (nM)*
- ≤ 1
- ≤ 10
- ≤ 100
- ≤ 1000
- > 1000
SECUKINUMAB
(CONSENTYX® – NOVARTIS)
Secukinumab

• 50,000 Foot View
  – Antibody injectable for moderate – severe plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis

• MOA
  – IL-17A monoclonal antibody

• Dosing
  – Psoriasis: 300 mg SC QWk x 5 doses, then Qmonth
  – AS/PA: 150 mg SC QWk x 5 doses, then Qmonth

• Increases risk of infection / Requires TB test
CANGRELOLR
(KENGREAL®-THE MEDICINE CO.)
Cangrelor

• Platelet inhibitor
  – Decreases risk of peri-procedural myocardial infarction during percutaneous coronary intervention (PCI)

• Mechanism
  – Direct-acting P2Y\textsubscript{12} inhibitor
    • Irreversibly inhibits ADP receptor

Nat Rev Cardiol 2011;8:547
Cangrelor

- IV administration
  - 30mcg/kg bolus 30 minute prior to PCI
  - 4mcg/kg/minute infusion during procedure
  - Continue at least 2 hours

Nat Rev Cardol 2011;8:547
Cangrelor

- Transition to oral agent
  - 600mg clopidogrel or 60mg prasugrel
    - Immediately at end of infusion; do NOT give prior to discontinuation of infusion
  - 180mg ticagrelor
    - Immediately at end of, or during infusion

- Rapid onset/offset
  - Do not use with gp IIb/IIIa P2Y_{12} inhibitor

Nat Rev Cardiol 2011;8:547
SACUBATRIL/VALSARTAN
(ENTRESTO®-NOVARTIS)
Neprilysin

- Degrades vasoactive peptides
  - Natriuretic peptides
  - Bradykinin
  - Others
Neprilysin Inhibition

- Increases natriuretic peptides & opposes neurohormonal activity
PARADIGM-HF

• HFrEF
  – LCZ696 (valsartan & neprilysin inhibitor) vs. enalapril

• Methods
  – Double-blind RCT
    • N = 8442 class II-IV HF
    • EF ≤ 40%
  – Primary outcome
    • Composite of CV death or hospitalization for HF

N Engl J Med 2014;371;11
PARADIGM-HF

• Results
  – Trial stopped @ mean f/u 27 months
  – Primary outcome
    • LCZ696 = 914 (21.8%) vs. enalapril = 1117 (26.5%)
      – Hazard ratio 0.80; 95% CI 0.73 to 0.87; P<0.001
  – LCZ696 group
    • > hypotension, non-serious angioedema
    • < renal impairment, hyperkalemia, cough

• Conclusions
  – LCZ696 superior to enalapril in reducing risk of death & hospitalization for HF

N Engl J Med 2014;371;11
Sacubatril & Valsartan (Entresto®)

• Potential to replace ACE inhibitor
  – Contraindicated with ACEI, pregnancy
  – HFrEF NYHA class II-IV
    • LVEF ≤40%
    • Stable
      – Symptomatic despite optimal therapy

• Dosing
  – Sacubatril/valsartan
    • 24mg/26mg=50mg (~40mg valsartan)
    • 49mg/51mg=100mg (~80mg valsartan)
    • 97mg/103mg=200mg (~160mg valsartan)
IVABRADINE
(CORLANOR®-AMGEN)
Heart Rate Control

• HFrEF patients
  – Elevated HR
    • Increase in morbidity & mortality

• Placebo group in SHIFT trial
  – Risk of CV death or HF hospitalization
    • 2.9% per 1BPM increase
    • 15.6% per 5BPM increase

• HR <60bpm vs. >75bpm
  – 32.4% decrease mortality & HF hospitalization
HR Regulation

• SA node produces “pacemaker” impulses
  – Spreads to AV node triggering ventricular contraction
• $I_f$ current
  – Initiates diastolic depolarization of SA node
Ivabradine

- $I_f$ inhibitor
  - Binds to HCN channels
    - “use dependent”
- SA node ($f$ channels)
  - Carries $I_f$ current
    - prolongs diastolic time
    - Inhibition reduces heart rate

- Retina ($h$ channels)
  - Carries $I_h$ current
    - Inhibition causes visual disturbances
Ivabradine

- Prolongs diastolic time
  - Inhibits $I_f$ current, reducing heart rate
- Increases stroke volume
  - Preserves myocardial contractility
  - BP
Ivabradine

- HFrEF patients
  - Elevated HR
    - Increase in morbidity & mortality
- HR ≥ 87 BPM
  - >2X risk for CV death or hospitalization for HF vs. HR 70-72 BPM
    - Hazard ratio 2.34, 95% CI 1.84–2.98, p < 0.0001
- Elderly HFpEF patients had symptomatic improvement & HR reduction
Ivabradine (Corlanor®)

• Approved to reduce hospitalization from HF
  – Consider in HFrEF
    • LVEF ≤35%
    • Resting heart rate
      – ≥70 BPM
    • On max dose of BB
      – Or intolerant

• Titrate to resting HR