Pharmacology Update: New Drugs in the Arsenal 2015 - 2016

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Objectives:
• Explain the basic pharmacology of at least three drugs that are unique molecular entities (as opposed to existing drugs with new indications, different dosage formulations or in fixed-dose combinations)
• Discuss possible advantages or disadvantages of three new medications compared to existing drugs in the same class.
• List newer approved indications or dosage formulations for existing drugs.

Disclosure:
The speaker has no financial or other conflicts of interest to disclose

Any mention of unlabeled uses for specific medications will be prefaced verbally to that regard

Cardiovascular

Entresto – sacubitril / valsartan
• Combination of Neprilysin inhibitor (blocks breakdown of BNP) and Valsartan (ARB)
• Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic heart failure (CHF) (NYHA class II-IV) and reduced ejection fraction
• Although BNP levels typically rise with increasing severity of HF, much of the measured BNP is ineffective biologically

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF
One Enzyme — Neprilysin — Degrades Many Endogenous Vasoactive Peptides

Endogenous vasoactive peptides (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactivemetabolites

Entresto – sacubitril / valsartan

Mechanisms of Progression in Heart Failure
Myocardial or vascular stress or injury

Increased activity or response to maladaptive mechanisms

Decreased activity or response to adaptive mechanisms

Angiotensin II

BNP Activity

Evolution and progression of heart failure

Entresto – sacubitril / valsartan

Mechanisms of Progression in Heart Failure
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Angiotensin II

Valsartan

Succubitril

BNP Activity

Evolution and progression of heart failure

Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily ↔ Enalapril 20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Risk (%)

Enalapril (n=4212)

Valsartan/sacubitril (n=4187)

HR = 0.80 (0.73-0.87)

P = 0.0000002

Number needed to treat = 21
**Pharmacology Update**

**PARADIGM-HF: Cardiovascular Death**

![Graph showing Kaplan-Meier Estimate of Cumulative Rates (%)](image)

**Enalapril** (n=4212)

- HR = 0.80 (0.71-0.89)
- \( P = 0.00004 \)
- Number need to treat = 32

**Valsartan/sacubitril** (n=4187)

**PARADIGM-HF: All-Cause Mortality**

![Graph showing Kaplan-Meier Estimate of Cumulative Rates (%)](image)

**Enalapril** (n=4212)

- HR = 0.84 (0.76-0.93)
- \( P < 0.0001 \)

**Valsartan/sacubitril** (n=4187)

**PARADIGM-HF: Summary of Findings**

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**Valsartan/sacubitril more effective than enalapril in . . .**

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by incremental 20%
- Reducing the risk of HF hospitalization by incremental 21%
- Reducing all-cause mortality by incremental 16%
- Incrementally improving symptoms and physical limitations

**PARADIGM-HF: Summary of Findings**

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**Valsartan/sacubitril better tolerated than enalapril . . .**

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema*

* Risk of angioedema ~ 1:200 with valsartan/sacubitril ~ 1:300 with ACEI

**Take home**

- Still not first line - continue to use standard regimen of an ACEI or ARB, beta-blocker, and an aldosterone antagonist in most patients.
- If no benefit in patients titrated to target doses of above, consider swapping out ACEI or ARB for valsartan/sacubitril – especially after a recent heart failure hospitalization
- But only in pts with systolic BP is > 100 mmHg
- High cost - approx $375/month.

**Angiotensin Neprilysin Inhibition Doubles Benefit on CV Death of Current Inhibitors of the RAS**

![Graph showing % Decrease in Mortality](image)
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

- Angiotensin receptor blocker
- ACE inhibitor
- Beta blocker
- Angiotensin neprilysin inhibition
- Aldosterone antagonist

% Decrease in Mortality

0% 10% 20% 30% 40%

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

PCSK9 Inhibitors and Cholesterol

Who may need PCSK9 Inhibitors?

- Statin intolerant
- Genetic disorder (FH)
- Uncontrolled on statins

1.2 Million Potential Targeted PCSK9 inhibitor population in U.S.

Life cycle of LDL receptors

Effects of PCSK9 inhibitor (mAb) on LDL Receptor Expression

Praluent (alirocumab)

- PCSK9 inhibitor (monoclonal antibody)
- Indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering
- Dosage - 75 mg administered sub-Q once every 2 weeks, of LDL-cholesterol (LDL-C).
- Side Effects
  - nasopharyngitis
  - injection site reactions
  - influenza

Repatha (evolocumab)

- PCSK9 inhibitor (monoclonal antibody)
- Indications – as adjunct to diet and maximally tolerated statin therapy
  - for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
  - as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
Repatha (evolocumab)
Dosages and frequency or administration (Sub-Q)
- In HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD - EITHER 140 mg q2 weeks OR 420 mg qMonthly.
- In patients with HoFH - 420 mg once monthly.

- Side Effects
  - nasopharyngitis
  - upper respiratory tract infection
  - influenza
  - back pain
  - injection site reactions

PCSK9 Inhibitors

“Pros”
Greater reduction in LDL Additive with Statins Useful in FH Well tolerated

“Cons”
Bi-weekly or monthly injections

COST: $14,000+/year

Direct Factor Xa inhibitors

Intrinsic pathway
Extrinsic pathway

Factor Xa inhibitors
Rivaroxaban
Apixaban
Edoxaban

Savaysa edoxaban tablets

- 3rd Oral Factor Xa inhibitor (4th NOAC)
- Once-daily dosing
- Approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Also to treat DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.

Savaysa edoxaban tablets
Clinical Trials
- Atrial Fib
  - Higher dose (60 mg) Savaysa similar to warfarin for the reduction (non-inferior) in the risk of stroke with significantly less major bleeding compared to warfarin.
- DVT / PE
  - 3.2 percent of participants taking Savaysa had a symptomatic recurrent VTE compared to 3.5 percent of those taking warfarin.

Savaysa edoxaban tablets
Boxed warnings:
1. Do not administer to nonvalvular atrial fibrillation (NVAF) patients with CrCl >95 mL/minute. In clinical trials, these patients had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin.
   - CrCl >95 mL/minute: Use is not recommended.
   - CrCl 51 to 95 mL/minute: No dosage adjustment
   - CrCl 15 to 50 mL/minute: 30 mg once daily
   - CrCl <15 mL/minute: Use is not recommended
2. Premature discontinuation of any oral anticoagulant, including edoxaban, in the absence of adequate alternative anticoagulation increases the risk of ischemic events.
**SGLT2 inhibitors**

- **Farxiga**
  - dapagliflozin
- **Jardiance**
  - empagliflozin

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes
- Lower A1C by about 0.7 – 1.0%
- May also decrease weight by about 4 to 7 pounds and modestly lower BP (3 – 5 mmHg)
- High costs ~ $9 – 10/day
- Consider as second or third-line options

**Farxiga**
- dapagliflozin

**Jardiance**
- empagliflozin

- Most common side effects:
  - Vaginal yeast infection (7 – 10%)
  - Balantitis (~5 - 6%) (uncircumsized > circumsized)
  - Urinary tract infection
    - All of the above more likely in those already at risk
  - Mild diuresis
  - Dose in AM due to potential diuresis

Because SGLT2 inhibition is associated with an osmotic diuretic effect, it can cause a reduction in intravascular volume leading to dehydration and orthostatic or postural hypotension

**SGLT2 inhibitors & Diabetic Ketoacidosis (DKA)**

- April 2016 - AACE and ACE report:
- No definitive evidence re SGLT2 inhibs causing DKA
- Majority of cases in insulin-deficient diabetics
  - Latent autoimmune diabetes
  - Type I diabetes (off label or new clinical trials)
- Other cases appeared to be precipitated by metabolically stressful event
  - Surgery, Extensive exercise, MI / Stroke
  - Severe infections, Prolonged fasting
  - Other stressful physical or medical conditions

**AACE Recommendations w SGLT2 inhibitors – AVOID:**

- Excessive alcohol intake
- Low carbohydrate diet
- Ketogenic diet
GLP-1 agonists

- Exenatide
- Exenatide ER
- Liraglutide
- Albiglutide
- Dulaglutide

Tanzeum
Trulicity

- Albiglutide
- Dulaglutide

- 4th, 5th, and 6th approved GLP-1 agonists
- Consider as possible add-on to metformin, gliptins, glitazones, sulfonylureas, insulin, etc.
- Albiglutide
  - Glp-1 coupled to human albumin + amino acid substitutions
  - Imparts DPP-4 resistance, allowing once-weekly dosing
- Dulaglutide
  - GLP-1 covalently linked to an Fc fragment of human IgG4,
  - Thereby protecting GLP-1 moiety from inactivation by DPP-4
- Lixisenatide
  - Exendin-4 peptide with addition of 6 lysines at the end

Lixisenatide (Adlyxin)

- ELIXA – 1st CV risk study of any GLP-1 agonist
- Concern over possible increase in risk for cardiovascular problems for class.
  - 6,068 subjects from 49 countries- lixisenatide vs placebo, with a follow-up period > two years.
- Outcomes- no increased risk for CV death, MI, stroke, unstable angina or heart failure in type 2 diabetes pts with recent ACS
- Also found no increase in pancreatitis or cancers and a modest benefit in terms of weight gain

GLP-1 agonists - comparison

- Subtle differences in A1c lowering, ease of use, weight loss, severity of side effects, cost

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>A1C Decrease</th>
<th>Weight Loss</th>
<th>Reconstitution required</th>
<th>Dosing Frequency</th>
<th>Cost/month</th>
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<tr>
<td>exenatide (Byetta)</td>
<td>1%</td>
<td>4 lbs</td>
<td>No</td>
<td>Twice DAILY</td>
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<td>6 lbs</td>
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<td>albiglutide (Tanzeum)</td>
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<td>dulaglutide (Trulicity)</td>
<td>1.5%</td>
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<td>No</td>
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</table>

Psychopharmacology

brexpiprazole (Rexulti)

- Approved for schizophrenia /adjunct for MDD
- Compared with aripiprazole:
  - More similar to other SGAs than aripiprazole
  - Theoretically more effective antipsychotic but larger risk of EPS and prolactin elevation, due to ~ 50% greater intrinsic activity at D2 receptors
  - High affinity for serotonin 5HT1A receptors (partial agonist) and 5HT2A receptors (antagonist) – benefit ?
  - Much less clinical experience – no head-to-head comparisons
  - Not currently approved for bipolar
  - Brand only – higher price!
brexpiprazole (Rexulti)

- Many potential drug interactions
- Cytochromes P450 3A4 and 2D6
  - Caution with inhibitors/inducers
  - Dosage reductions specified in Packaged Insert
  - May be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine)
- Side Effects: akathisia, weight gain, headache, and somnolence. Mean weight gain over 6 weeks was 1.0-1.3 kg greater with brexpiprazole 2 mg/day than with placebo.

cariprazine (Vraylar)

- FDA-approved indications
  - Treatment of schizophrenia
    - Starting dose: 1.5 mg/day
    - Recommended dose: 1.5 mg to 6 mg/day
  - Acute treatment of manic or mixed episodes associated with bipolar disorder
    - Starting dose: 1.5 mg/day
    - Recommended dose: 3 mg – 6 mg/day
- Starting dose: 1.5 mg/day
- Recommended dose: 3 mg – 6 mg/day
- Partial agonist at:
  - D2 receptors
  - D3 receptors
  - 5-HT1A receptors
- Antagonist at:
  - 5-HT2B receptors
  - 5-HT2A receptors
- Antagonist at (moderate to low affinity):
  - H1 receptors
  - 5-HT2C receptors
- It has been suggested that 5-HT1A, 5-HT2B and D3 receptor effects could improve negative symptoms via activation of DA neurotransmission in frontocortical regions. To date, no conclusive data from RCTs support this!
- Although the targeting of the D3 receptor was thought to reduce the likelihood of extrapyramidal symptoms, they are still common with this drug.

New Stimulant Formulations for ADHD

Methylphenidate
  - Aptensio XR
    - 1st 12-hour sprinkle cap
  - QuilliChew ER
    - 1st 8-hour chewable tab
Amphetamine
  - Adzenys XR-ODT
    - new once-daily ER forms - orally disintegrating tab
  - Dyanavel XR
    - first suspension

Gastrointestinal
Viberzi (eluxadoline)
- Mu-opioid receptor agonist and delta-opioid receptor antagonist.
- In vivo studies indicate that the activity of eluxadoline at the two different opioid receptors controls GI function as well as decreases pain and potentially mitigates the constipating effect of unopposed mu agonism.
- Specifically indicated in adults for the treatment of irritable bowel syndrome with diarrhea

Viberzi (eluxadoline)
- Dosing:
  - Patients with a gallbladder: 100 mg twice daily; may decrease to 75 mg twice daily in patients unable to tolerate the 100 mg dose.
  - Patients without a gallbladder: 75 mg twice daily.
  - Patients taking cyclosporine, gemfibrozil, atazanavir, Protease Inhibitors): 75 mg twice daily.
- Avoid concurrent use with: Alcohol, Anticholinergics, opioids, alosetron (Lotronex)
- Adverse effects:
  - Constipation, nausea, abdominal pain

Xifaxan (rifaximin)
- Semisynthetic rifamycin derivative and non-systemic gastrointestinal site-specific broad spectrum antibiotic
- Inhibits of bacterial protein synthesis and consequently inhibits the growth of bacteria.
- Recent evidence suggests that patients with IBS may have an alteration in gastrointestinal flora.
  - Specifically, findings suggest that patients with IBS have excessive bacteria in the small bowel, known as bacterial overgrowth (SIBO). Up to 50% of patients with IBS may have SIBO.
- Alleviated symptoms in patients with IBS who were LBT positive and improvement was observed for a period of 3 months after 2 weeks of treatment with rifaximin [Schoepfer, Aliment Pharmacol Ther. 2012]
- Recurrence of SIBO documented in 12.6% of patients at 3 months, 27.5% of patients at 6 months and 43.7% of pts at 9 months. [Lauritano et al. Am J Gastroenterol 2008]
  - Results suggest that there is the need for further treatment courses in many patients
- Recommended Dosing: 550 mg PO 3 times daily for 14 days; may be retreated up to 2 times with the same dosing regimen if symptoms recur.
- Cost ~ 550 mg (60): $2200

Miscellaneous

Belsomra suvorexant
- 1st approved drug in class - orexin receptor antagonist
- Available in 5, 10, 15, and 20 milligrams
- Dosed once per night within 30 minutes of bedtime
- Three clinical trials showed decreased sleep latency & increased sleep maintenance (compared to placebo)
- Most common SE – next-day drowsiness / diving issues
- Cleared by CYP3A4 – not recommended with
  - Strong 3A4 inhibitors / liver impairment
- Schedule IV
- Same boxed-warning as all other sleeping pills re: complex behaviors including sleep-walking, driving, talking, eating,
Opioids

• Xtampza ER
  – Oxycodone (bid) – capsules can be broken and microspheres emptied into feeding tube or sprinkled onto soft food or directly into mouth
• Belbuca
  – ER/LA sublingual film buprenorphine that is dissolved in the mouth and absorbed through the inner lining of the cheek. C-III.
• Oxayo
  – first and only IR oxycodone designed to discourage abuse via the route of snorting - contains an inactive ingredient that may cause nasal burning tablet is crushed
• Relistor (PO)
  – oral formulation of methylnaltrexone approved opioid-induced constipation (OIC) in adults with chronic noncancer pain. Efficacy similar to SC form.

Addyi - flibanserin

• “Failed antidepressant . . . But some women in the trials reported experiencing a “slight” increase in sexual desire
• Pharma company sought new indication approval – DSM 5: Female sexual interest/arousal disorder.
• Full agonist at 5-HT1A receptor (kicks up NE and DA in frontal cortex) and antagonist of the 5-HT2A receptor (decreases serotonin activity)
  – Dizziness, somnolence, nausea, fatigue, insomnia, dry mouth
• Boxed warning label – The use of Addyi and alcohol increases the risk of severe hypotension and syncope; therefore, alcohol use is contraindicated.
• Available only through a restricted program called the Addyi REMS Program.

Thank you for listening

Alan

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