New Drugs on the Market
Drug Updates for 2015-2016

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Learning Objectives

1. Examine the use of elected new pharmaceutical agents available for clinical practice.
2. Summarize the benefits, risks, and alternatives of selected new pharmaceutical agents.

2015 Was A Busy Year

- FDA approved 45 novel new drugs and biologics
- The 10-year average is 28 novel new drugs per year
- This is the highest in 19 years
- For comparison the most ever approved was 53 in 1996
- Of the 45 approved
  - 22% were considered breakthrough therapies
  - 31% were fast tracked
  - 36% were approved as the first drug within a class

Cardiovascular

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AES Question

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AES Question 1

What approximate percentage reduction in LDL was noted in heterozygous familial hypercholesterolemia (HeFH) in the clinical trials involving PCSK-9 inhibitors?

A. 20%
B. 40%
C. 60%
D. 80%

PCSK9 Inhibitors

- These are monoclonal Abs that bind to proprotein convertase subtilisin kexin type 9 and inhibit binding of PCSK9 to LDLR freeing up more receptors to hepatically clear LDL and lower the level
- Cost: Estimated at $10,000/annually
  - Both companies have a system in place to assist with prior authorization
- Two on market
  - Alirocumab (Praluent)
  - Evolocumab (Repatha)
- Clinical Efficacy is approximately 60%
  - ODYSSSEY trials
  - OSLER 1 and 2

Alirocumab (Praluent)

- Indication:
  - Adjunct to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (HeFH) or CV disease who require additional lowering of LDL
- Dose:
  - 75 mg SC q 2 weeks with increase to 150 mg q 2 weeks if LDL goal not achieved at lower dose
- Safety:
  - Well tolerated, but studies ongoing
  - Refrigerated, then warmed over 30 minutes before administered

Evolocumab (Repatha)

- Indications:
  - Same as Praluent except it is also indicated for homozygous familial hypercholesterolemia (HoFH)
- Dosing:
  - 140 mg SC q 2 week or 420 mg q month
  - HoFA only the 420 mg SC q month is indicated
  - 420 mg dose is 3 consecutive SC injections within 30 minutes
- Efficacy:
  - Of note in HoFH there was only a 30% reduction in LDL
- Safety:
  - Refrigerated then warmed to room temperature over 30 minutes before administration in abdomen, thigh, or upper arm
  - Studies ongoing, but appears well tolerated

Edoxaban (Savaysa)

- Factor Xa inhibitor
- Indication:
  - Prevention of thromboembolism in nonvalvular afib patients with CrCl ≤ 95 mlLmin
  - VTE treatment after 5-10 days of parenteral anticoagulant
- Dose:
  - Afib and VTE: 60 mg/d unless CrCl 15-50 mL/min or weight <60 kg then 30 mg/d
- Efficacy:
  - About as effective as warfarin in afib and VTE management
  - Not as effective as warfarin when CrCl >95 mL/min
- Safety:
  - 6 fewer bleeds per 1000 pt year in afib management
  - 18 fewer bleeds per 1000 pt year in VTE treatment

Idarucizumab (Praxbind)

- Humanized monoclonal antibody fragment that binds dabigatran
- Indication:
  - Immediate reversal of dabigatran for urgent/emergent situations
- Dosing:
  - 5 g dose but given as two 2.5 g/50 mL bolus within 15 minutes of each other, can be redosed based on continued bleeding
- Efficacy:
  - RE-VERSE AD trial showed 90-100% immediate reversal within 4 hours
  - Dabigratran can be restarted 24 h after the reversal dose given
- Safety:
  - Hereditary fructose intolerance could lead to anaphylactic reactions
  - Thrombosis risk increases
  - Other side effects were generalized
- Cost:
  - $3500/5 g dose

Sacubitril and Valsartan (Entresto)

- New class called neprilysin inhibitor + ARB
  - Increases natriuretic peptides, bradykinin, adrenomedullin allowing for more vasodilation and sodium loss and less hypertrophy. Improves the pathophysiology abnormalities of HF
- Indication:
  - NYHA Class II-IV with reduced EF in place of ACE-I or ARB
- Dose:
  - 49/51 mg BID titrated q 2 weeks to target of 97/103 mg BID
  - 103 mg of valsartan = 160 mg due to different salts
  - 24/26 mg BID is starting dose for ACE-I or ARB naive
- Efficacy:
  - PARADIGM-HF showed statistically significant lower hospital admissions and mortality vs ACE-I (26.5% vs. 21.8%), but trials did not have many African-Americans participating
- Safety:
  - Hypotension, angioedema, hyperkalemia, cough, dz, and renal failure
  - Neprilysin helps degrade beta amyloid plaque….if inhibit this, could it lead to dementia?
- Cost:
  - $450 per month

Ivabradine (Corlanor)

- Works by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the pacemaker called the funny current. Predominate effect seen at SA node
- Indication:
  - CHF with EF ≤35% and in NSR with resting HR ≥70 bpm and who are on maximally tolerated doses of beta-blocker
- Dose:
  - 5 mg BID with meals, adjusted in 2 weeks to resting HR 50-60 bpm
  - Maximum dose is 7.5 mg BID
- Efficacy
  - SHIFT trial
  - Showed 18% drop in risk for CV death or hospitalization for worsening HF over 23 months
- Safety:
  - Bradycardia, a fib, heart block
  - Do not use with CCB, grape fruit juice, or drugs that cause prolonged QT
- Costs:
  - $450 for both doses

Infectious Disease

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AES Question

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AES Question 2

Why did the ACIP classify use of the Meningococcal B vaccine for routine use in 16- to 18-year-olds as a level B recommendation?

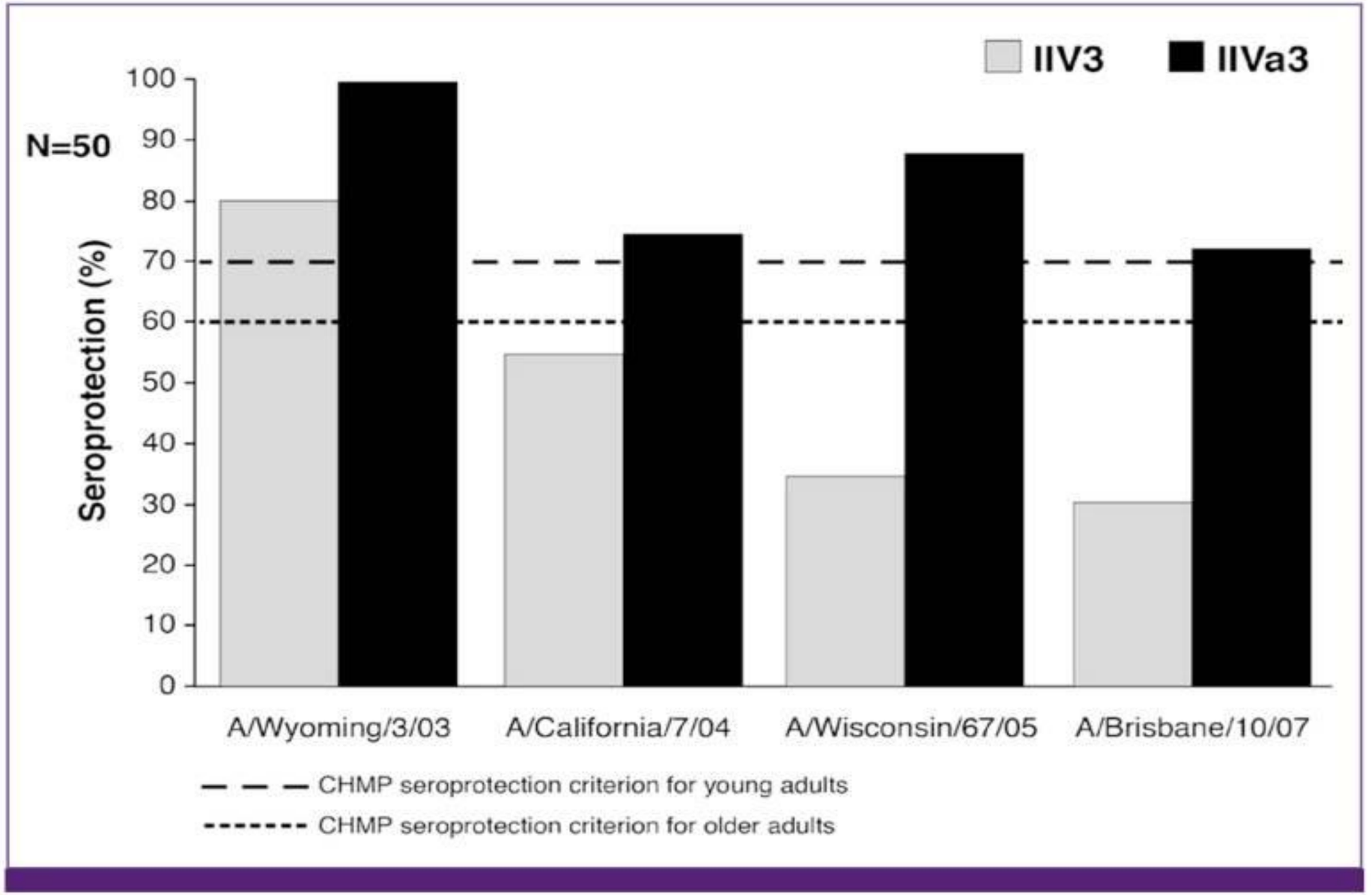
A. Lack of efficacy
B. Increased safety concerns
C. Limited availability
D. Not cost effective

Meningococcal B (Bexsero and Trumenba)

- Prevention of Serogroup B meningococcal disease
- Indication:
  - Ages 10-25 yo with complement d/o; asplenia; sickle cell; increased risk
  - ACIP did not recommend routine vaccination but did narrow age to 16-23 yo with emphasis on 16-18 yo via a B recommendation because not cost effective
- Dose:
  - Bexsero – two-dose series (0 and 1-6 mos)
  - Trumenba – three-dose series (0, 2, 6 mos)
  - They are NOT interchangeable
- Efficacy:
  - Titers are increased, but clinical outcome data is not available yet
- Safety:
  - Anaphylaxis (1 case out of 11,000 and 1 case out of 59,000)
- Costs:
  - Approximately cost is $350 per series

Influenza Vaccine (Fluad)

- Revved up trivalent influenza vaccine that contains an adjuvant oil-in-water emulsion of squalene oil that enhances or directs the immune response.
- Indication:
  - Patients 65 yo and older
  - Potentially could be used for immunosuppressed
- Dose:
  - 15 µg of purified hemagglutinin (HA) surface antigen subunits
  - Formulated with MF59C.1 (each 0.5 mL dose contains: squalene 9.75 mg, polysorbate 80 1.175 mg, sorbitan trioleate 1.175 mg, sodium citrate 0.66 mg, citric acid 0.04 mg and water for injection)
- Efficacy:
  - Multiple international trials show higher antibody responses, and 2013 trial stated there was a 25% reduction in hospitalizations and cases of pneumonia
- Safety:
  - Injection site reaction, tenderness, muscle aches, and fatigue reported
- Cost:
  - Not available at time of research


IIV3
IIVa3
N=50
Seroprotection (%)
100
90
80
70
60
50
40
30
20
10
0
A/Wyoming/3/03
A/California/7/04
A/Wisconsin/67/05
A/Brisbane/10/07
CHMP seroprotection criterion for young adults
CHMP seroprotection criterion for older adults

HPV 9 Vaccine (Gardasil)

- Additional guidance on use of 9-valent HPV vaccine was issued in 2016
- Indication updated:
  - Men and Women ≥9 yo and ≤26 yo
- Dosing:
  - Remains 3-shot 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

Endocrine

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Insulin Glargine (Toujeo)

- Long-acting insulin analog but higher concentration of 300 u/mL vs 100 u/mL of Lantus
- Indication:
  - Type 1 or Type 2 Diabetes
- Dose:
  - Type 1 insulin naïve start 30-50% of total dose based on 0.2-0.4 u/kg
  - Type 2 insulin naïve start 0.2 u/kg
  - Changing insulin therapy requires a 1:1 conversion if once daily insulin + 10% increase
  - If BID insulin then only use 80% of dose for Toujeo
- Efficacy:
  - Noninferior to Lantus in lowering BS, does have a smaller depot and absorption is slower, allowing for a more consistent lowering
  - Takes up to 5 days to see effect, so dosing adjustments cannot happen daily
- Dosage Form:
  - Solostar pen with 1.5 mL lasting about 28 days
  - Cost $335
  - Lantus is going generic soon but UHC will be converting all patients to this formulation by 2016

Insulin Degludec (Tresiba)

- New insulin formulation that is latest attempt to find the most physiologic replacement for absent or insufficient basal insulin secretion
- Indication:
  - Type 1 and Type 2 Diabetes
- Dosing
  - Type 1 insulin naïve start 30-50% of total dose based on 0.2-0.4u/kg
  - Type 2 insulin start 10 units/day
  - Already on insulin it is a 1:1 conversion of daily doses
- Efficacy
  - True once a day insulin that can be given at any time of the day with titration every 3-4 days
  - Non-inferior to other insulins – not any better efficacy but more convenient for dosing
  - Appears to have less hypoglycemia than other “long-acting” insulins
- Dosage forms:
  - 300 u (110u/mL) pens with 5 pens per pack
  - 600 u (200u/mL) pens with 3 pens per pack
  - $440-530 per pack

Controlled Substances

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AES Question

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AES Question 3

Which of the following patients has a relatively low risk for opioid overdose?

A. Opioid-naïve; new prescription for 10 mg morphine equivalents per day
B. History of alcoholism; receiving opioid prescription from 2 different prescribers
C. Opioid-dependent; taking 100 mg morphine equivalents per day
D. Taking an opioid in combination with an antidepressant and a sleep medication

Naloxone (Evzio or Narcan)

- New dosage forms are emerging for “community use”
  - IM has two self-contained auto-injectors each with 0.4 mg (talks person through the administration)
  - IM NON auto-injector is now available in several states BTC
  - Intranasal has two 2 mg/2 mL SYRINGES prefilled (no inhalation needed)
- Indication:
  - Initial treatment of an opioid associated life-threatening emergency to be used after CPR has been initiated
- Dosing:
  - *IM formulation*: inject 0.4 mg, can repeat in 2-3 minutes
  - *Intranasal formulation:* spray ½ of 2 mL syringe into each nostril, can repeat in 2-3 minutes
- Efficacy:
  - Estimated that 1 life is saved for every 164 kits distributed
  - Between 1996 & 2010, 53,000 people were trained and they reversed >10,000 opioid overdoses
- Safety
  - Acute withdrawal symptoms occur i.e. vomiting, agitation, anxiety, diarrhea
- Cost:
  - $125 intranasal
  - $2250 Evzio however 0.4mg/ml non auto-injection is $18.71

Naltrexone (Vivitrol)

- Indication:
  - Maintenance of sobriety that is initiated at least 7-10 days AFTER person is opioid free. Approved in 2013 but timely so wanted to include in the discussion
- Dosing:
  - Suspension version is 380 mg IM monthly
- Efficacy:
  - 36% of pts refrained from opioid use for 6 months vs 23% in placebo group
  - More likely to stay in treatment programs
  - Reported less craving
  - Were less likely to relapse to physical dependence
- Safety:
  - Common side effects: nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps
  - Serious side effects: injection site reactions, liver damage
- Cost:
  - In office injection: Reimbursement rates vary

Women’s Health

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AES Question

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AES Question 4

Which of the following women may be a candidate for use of flibanserin (Addyi) for sexual dysfunction?

A. 36 yo with three children and currently seeking counseling for self-image issues
B. 63 yo who has been married to her husband for 30 years and is deeply in love but intercourse is painful
C. 40 yo who is experiencing intimacy issues with her husband after the recent birth of her 3rd child
D. 28 yo who enjoys an active social life out at the bars and clubs but has not had an orgasm since starting fluoxetine 6 months ago.

Flibanserin (Addyi)

- Works by increasing dopamine and norepinephrine and decreasing serotonin
- Indication:
  - First drug indicated for acquired hypoactive sexual desire disorder caused by distress or interpersonal difficulty
  - Only pre-menopausal women
  - Not for use in psychiatric, medication, or relationship problems
- Dosing:
  - 100 mg nightly x 8 weeks and if no improvement D/C
- Efficacy:
  - 1 out of 11 women reported an increase of 0.5 to 1 additional satisfying sexual events per month vs placebo
  - Earliest impact was seen was after 4 weeks of use
  - 1 of 4 clinical trials show statistically significant results

Flibanserin (Addyi)

- Safety:
  - Most commonly reported were dizziness, somnolence, nausea, and fatigue (sedation)
  - Hypotension is a big concern
- Drug Interactions:
  - CYP 3A4 and 2C19 inhibitors increase level of this drug potentiating the side effects mentioned
  - Contraindicated with other 3A4 drugs such as amiodarone, amlodipine, fluoxetine, verapamil
  - CANNOT be used with alcohol or any other CNS depressant
- Cost:
  - $350/month

Gout

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Lesinurad (Zurampic)

- URAT1 inhibitor blocks the reabsorption of uric acid in the kidneys
- Indication:
  - To be used in conjunction with xanthine oxidase inhibitors (XOIs) when target uric acid levels have not been achieved with monotherapy
- Dosing:
  - 200 mg daily
- Efficacy:
  - CLEAR 1, CLEAR 2 and CRYSTAL trials all showed lower UA levels after a year with combination therapy vs monotherapy
  - Mean gout flare rates were not effected per CLEAR trials
  - Complete resolution of a least one tophus was not achieved in CRYSTAL
- Safety:
  - HA, heartburn, cannot use in CKD 5 and/or ESRD or renal transplant pts
  - Did have an increase in SCr at higher doses
  - Black Box warning: may cause ARF at higher doses or as monotherapy

Did Not Make the Show

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Approved in 2015-2016

- Apensio XR - Methylphenidate
- Dyanavel XR – Amphetamine
- Stiolto – combo LABA/LAAC
- Seebri – LAAC DPI
- Utibron – LAAC/LABA
- Spiriva Respimat – asthma indication
- Glyxambi – SGLT2/DPP4 inhibitor
- Synjardy – SGLT2/Metformin
- Nucala – mAb for asthma
- Veltassa – potassium binder
- Viberzi – IBS-D
- Aristada – extended release abilify
- Vrayler – atypical antipsychotic
- Rexulti – atypical antipsychotic
- Kengreal – antiplatelet for PCI
- Genvoya – 5 drug combo for HIV

Best Practice Recommendations

- This past year the FDA approved more new entities than in the last decade
- 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?!

Answer Key

1. C
2. D
3. A
4. C

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