HOW DO YOU SPELL THAT?

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DISCLOSURE

• I am NOT a pharmacist or pharmacologist
• I don’t work for or knowingly invest in pharmaceutical or medical device companies
• I do work for medical journals, UpToDate, CME publishers, and the National Board of Medical Examiners, but I won’t be promoting them today.
• I will bring up a few off-label uses—can’t do a talk on new drugs without that!

WHAT THIS TALK ISN’T

• alirocumab
• brexipiprazole
• canregleror
• caniprazine
• ceftazidime-avibactam
• daclatasvir
• dinutuximab
• edoxaban
• eluxadoline
• evolocumab
• fibanserin
• idarucizumab
• insulin degludec
• isavuconazonium
• ivabradine
• lenvatinib
• lumacaftor
• palbociclib
• rolapitant
• sacubitril/valsartan
• secukinumab
• sonidegib
• trifluridine and tipiracil
• uridine triacetate
WHAT WE WILL BE TALKING ABOUT

- New drugs in the pipeline
- New drugs on the market
  (including a few from the preceding slide)
- Important drug updates
- Drugs? Where we're going we don't need drugs.
- The 2015 pharmanure list

The Twitter Experiment

Tweet questions to me:
@clknight

Why I’m doing this
New drugs in the pipeline

NILOTINIB FOR PARKINSON DISEASE

- Tyrosine kinase inhibitor used for CML
- Phase 1 study of biomarkers in CSF: 12 pts with advanced PD/LBD treated with low dose nilotinib for 6 months
- 11/12 showed improvement in symptoms; CSF biomarkers of neurodegeneration also improved
- Able to reduce meds during study, but symptoms worsened afterwards despite resuming meds
- Abstract presentation; months before publication
- Phase 2 trial expected in 2016

HERPES ZOSTER VACCINE THAT WORKS

- Recombinant/adjuvant vaccine (not live virus)
- Placebo-controlled RCT: 15,411 pts > 50 y/o
- 3.2 yr f/u: 210 cases of zoster in placebo group vs 6 in vaccine group
- Efficacy 96-98% in all age groups

New drugs on the market

A QUICK NOTE ON PRICES

- Prices come from goodrx.com
- GoodRx and LowestMeds negotiate discounts with pharmacies in return for sending them business
- Prices listed are lowest prices at local Seattle participating pharmacies and include discount
- Discounted price may be better or worse than cost to patient with insurance and/or manufacturer coupon
- Prices I’m giving are for a 30-day supply or a single course of therapy
PRICE COMPARISONS

<table>
<thead>
<tr>
<th></th>
<th>GoodRx low</th>
<th>GoodRx high</th>
<th>Costco</th>
<th>Bartell’s</th>
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<tbody>
<tr>
<td>Saxenda 3 mg x 30</td>
<td>$1070</td>
<td>$1175</td>
<td>$1300</td>
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<td>Sildenafil 20 mg x 30</td>
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<td>$272</td>
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</tr>
</tbody>
</table>

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PCSK9 INHIBITORS FOR HYPERLIPIDEMIA

- PCSK9 discovered 2003: degrades hepatic LDL receptors
- 4465 patients randomized to subcutaneous evolocumab vs placebo [+ usual tx]
  - 50-60% reduction in LDL; 53% reduction in CV events (NNTc 81)
- Similar data for alirocumab; both very expensive


DACLATASVIR FOR HCV GENOTYPE 3

- Previous NS5A inhibitors all genotype 1 specific; sofosbuvir/ribavirin regimen is 24 wks, tough to take, 84% effective
- Open-label trial, 12 weeks of daclatasvir/sofosbuvir in 151 pts: 90% SVR in treatment-naive patients, 86% in previously treated
- SVR rate 96% in patients without cirrhosis, but on only 63% with cirrhosis

UW Medicine  http://pmid.us/25614962
**VALSARTAN/SACUBITRIL FOR HFREF**

- Neprilysin inhibitor: reduces breakdown of vasodilatory peptides
- 8442 pts with class II-IV CHF, EF <40% randomized to valsartan/sacubitril vs enalapril for 27 months
- HR for death/CHF admission 0.80, NNTc 47
- Lots of potential, cost a concern

[http://pmid.us/25176015](http://pmid.us/25176015)

**IVABRADINE FOR HFREF**

- Acts to decrease HR at SA node without other cardiovascular effects
- Placebo-controlled RCT of 6558 pts, class II-IV, EF ≤ 35%, HR ≥ 70, followed for median 23 months
- Reduced HF hospitalizations (NNTc 38), HF-specific mortality (NNTc 96)
- No difference in all-cause or total CV mortality
- Critiqued because of low doses of β-blockers in study population: only 26% at guideline target dose

[http://pmid.us/20801500](http://pmid.us/20801500)

**SELEXIPAG FOR PULMONARY HTN**

- Oral prostacyclin agonist (similar mechanism to Flolan or Remodulin) for pulmonary hypertension
- Placebo-controlled RCT of pts with idiopathic and some secondary pulmonary HTN; some treatment-naive and some on oral meds (endothelin antagonists, PDE5 inhibitors); median tx 70 wk.
- Primary endpoint composite of disease progression, hospitalization, death: 27% in tx group vs 41% in placebo group; NNTc 10
- Trend toward reduction in mortality

[http://pmid.us/26699168](http://pmid.us/26699168)
9-VALENT HPV VACCINE

- HPV serotypes in 4-valent HPV vaccine cause 70% of cervical cancer, 90% of warts
- Additional 5 serotypes in HPV-9 cause additional 15-20% of cases of cervical cancer
- 5 yr trial of 9-valent vs 4-valent in women 16-26 y/o: 40% reduction in high-grade HPV disease (all serotypes) and 100% for vaccine serotypes (NNT 550)
- Reduction only present if HPV-negative when vaccine given

SUVOREXANT FOR INSOMNIA

- New neurobiology: orexin neurons in hypothalamus maintain wakefulness—decreased in narcolepsy
- Suvorexant is orexin antagonist with 2 hr peak, 12 hr elimination half life; metabolized by CYP3A4
- 1 year randomized trial with 30-40 mg showed continued efficacy/safety for one year; major adverse effect was somnolence (13%); also rare cataplexy (partial paralysis)
- FDA trials noted impaired driving day after 20 mg dose, recommended 5-10 mg initial dose

INHALED INSULIN

- Technosphere™ dry powder prandial insulin
- Superior to placebo, non-inferior to injectable insulin
- 27% cough; need to follow FEV1 annually
- Don’t use in COPD, asthma, smokers
**ELUXADOLINE FOR IBS-D**

- µ opioid agonist targeting receptors in the gut
- Unpublished data submitted to FDA:
- 12% difference (22% -> 34%) in diarrhea (p < .05)
- 3% difference (40% -> 43%) in abdominal pain response (p = NS)
- 8% difference (19% -> 29%) in composite of both (p < .05)

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http://fda.gov

**NEW ANTIDOTE FOR ACE ANGIOEDEMA**

- Icatibant is bradykinin antagonist used for hereditary angioedema
- Tiny (30 patients) RCT of icatibant vs steroids/antihistamines for ACE angioedema showed faster (8 vs 27 hr median time) and more complete resolution of symptoms
- No major adverse events other than tenderness at injection site
- Single dose used in this study retails for $10,000; best to reserve for scariest cases

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**ANTIDOTES FOR NEW ANTICOAGULANTS**

- Idarucizumab is anti-dabigatran monoclonal Ab able to pull it off of thrombin
- Ongoing study: report of 90 patients with either acute bleeding or need for emergent surgery showed rapid reversal of clotting time, no adverse events
- Andexanet is custom “decoy” protein: non-functional factor Xa that still binds FXA inhibitors
- Study in volunteers without need for anticoagulation showed rapid reversal with bolus + 2 hour drip

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Drug updates for 2015

STEROIDS FOR PNEUMONIA

• 2 placebo-controlled RCTs published 2015
• For severe pneumonia and CRP > 150, 5 days methylprednisolone 0.5 mg/kg reduced treatment failure (shock, intubation, death, progression on CXR) by 66% (NNT 5/episode)
• For all-comers CAP, 7 days of prednisone 50 mg decreased time to stable VS, SpO2 ≥ 90% by 1.4 days
• Hyperglycemia increased in both tx groups


ON-DEMAND HIV PROPHYLAXIS

• Daily pre-exposure prophylaxis (PrEP) with TDF-FTC (Truvada) reduces risk of transmission by 67% in heterosexual partners but only 44% in male partners of other men
• Placebo-controlled RTC of 4-dose “on-demand” TDF-FTC with unprotected sex: 2-24 h before, 24 & 48 h after
• 86% reduction in transmission of HIV in treatment group (7% vs 1%, NNTc 13)
• 2 cases of HIV in treatment group didn’t take meds

**DRY POWDER ALBUTEROL**

- Breath actuated dry powder inhaler
- Decreases timing/spacing issues with conventional propellant MDI
- Priced similar to HFA MDI (for now)
- May be more difficult for patients to use when acutely short of breath; good for albuterol prophylaxis (e.g. before exercise)

**ASPIRIN TO PREVENT RECURRENT VTE**

- Ample evidence that patients with unprovoked VTE are at higher risk of recurrence after anticoagulation
- Pre-specified post-hoc analysis of two earlier trials of aspirin 100 mg/d to prevent recurrent VTE after completing warfarin anticoagulation; avg 2 yr f/u
- 32% reduction in recurrent VTE (NNTc 42)
- Bleeding events rare in both groups, no significant difference (0.7% vs. 1.1%)

**SHOULD WE EVER BRIDGE WARFARIN?**

- Cohort study of 1812 pts on chronic warfarin for recurrent VTE prevention: Bleeding in bridge group much more common (HR 17.2, p < 0.01) with no significant difference in VTE
- Placebo-controlled RCT of 1884 pts with chronic AF: 0.1% decrease in arterial embolism (p = 0.01 for non-inferiority), 1.9% increase (RR 2.4, NNT 53) in major bleeding with LMWH bridging
- Should use bridging only in very high-risk situations
IVERMECTIN FOR ROSACEA

• Demodex mites may play a role in pathogenesis of rosacea; ivermectin has both anti-parasitic and anti-inflammatory properties

• RCT topical ivermectin vs metronidazole in 962 pts with papulopustular rosacea

• Slight edge to ivermectin in clearing skin lesions (84.9% vs 75.4%), NNT 10

SPIRONOLACTONE FOR RESISTANT HTN

• Randomized crossover trial of 335 pts with SBP > 140 to spironolactone/bisoprolol/doxazosin/placebo (in rotation) as 4th drug.

• SBP decrease 12.8 with spironolactone vs 8.5 with other two drugs vs 4.1 with placebo

SPIRONOLACTONE + TMP/SMX=DEATH

• Spironolactone & triamterene both inhibit potassium excretion by the kidney

• Canadian case-control study of 11,968 pts over 66 y/o who died of SCD while on spironolactone

• 328 patients were on antibiotics within 14 days of death; OR for TMP/SMX exposure was 2.46 compared to amoxicillin
**EZETIMIBE: IT'S BAAAAACK**

- Double-blind RCT of 18,144 pts with ACS randomized to simvastatin 40 mg with ezetimibe 10 mg vs placebo

- 7yr f/u: 32.7% composite MACE in ezetimibe group vs 34.7% in control (NNTc 350, HR 0.94)

- IVUS study showed increased atheroma regression with atorvastatin

(Images and references: [UW Medicine](http://pmid.us/26039521), [UW Medicine](http://pmid.us/26227186))

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**HA (SYNVISC, ETC) KNEE INJECTIONS: HIGH VALUE OR CASH COW?**

- Systematic review of 19 trials (4485 patients) of hyaluronic acid (HA) injections for knee DJD.

- 14 trials were placebo (sham) controlled; others had active or "usual care" controls

- Aggregate difference in all trials was about half of what most consider clinically important improvement

(Images and references: [UW Medicine](http://pmid.us/26677239))

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**DEXTROMETHORPHAN/QUINIDINE FOR ALZHEIMER DISEASE WITH AGITATION**

- Dextromethorphan/quinidine combination released in 2011 to treat emotional lability (pseudobulbar affect) in pts with ALS and MS

- 2015 placebo-controlled RCT in patients with Alzheimer dementia and agitation: agitation/aggression scores decreased by 1.5 points more on 12 point scale but with increase in fall risk (8.6% vs 3.9%)

- Quinidine dose (10 mg BID) is 1/40th of anti-arrhythmic dose; inhibits CYP2D6 and increases dextromethorphan activity 20-25 fold

(Images and references: [UW Medicine](http://pmid.us/26393847))
Nicotinamide (vitamin B3) has biological activity that reduces DNA damage from UV radiation. Australian RCT of adults with at least two non-melanoma skin cancers (NMSC) in previous 5 years and no other major risk factors: 500 mg nicotinamide bid vs matching placebo. Rate of new NMSC in next 12 months was 1.8 per person in tx group vs 2.4 per person in placebo group: approximately 1 lesion prevented for every two patients treated. Also 20% reduction in AK counts.

Hey! Those aren’t drugs!
TEXT MESSAGES FOR HEART DISEASE

- Australian RCT, 710 pts with CAD, 4 texts/week x 6 months vs usual care
- Text group had lower LDL (5 mg/dL), SBP (7.5 mmHg), and BMI (1.3 kg/m²); higher physical activity and smoking quit rates
- Durability of effect unclear

CBT FOR INSOMNIA

- CBT-I is a popular behavioral intervention for insomnia with an online version
- Meta-analysis of 36 small studies (n=15-200) of CBT-I sessions in pts with comorbid medical/psychiatric illness
- Insomnia remission in 36% of CBT-I pts vs 16.9% of controls; pooled odds ratio 3.28, p < 0.001
- Online version not tested in this trial; other small trials suggest it may help

KINESIO TAPE FOR LBP

- Open label RCT of elastic tape q 4 days x3 for acute/subacute LBP
- Pain improved earlier in tape group, less APAP use
- Outcomes similar at 4 wk
- Compare to JAMA study (26501533) showing no benefit with adding opioids to NSAIDS
**MUSIC, GUM, NOT SPIROMETRY POST-OP**

- 3 different studies in post-op patients:
  - Music reduced pain, anxiety, analgesia use
  - Chewing gum reduced time to first flatus/BM, LOS
  - Small RCT: no benefit with incentive spirometry


**SKIP THE STOCKINGS AFTER DVT**

- Systematic review of 5 trials (1418 patients) with proximal leg DVT: do compression stockings help?
  - No difference in rates of post-thrombotic syndrome, recurrent DVT or death
  - Largest trial (804 patients) had a non-compression placebo stocking and negative results

[UW Medicine](http://pmid.co/26747198)

**The PharManure list**

[UW Medicine](#)
DRUGS THAT MAKE ME GRUMPY

• Jublia & Luzu: New antifungals: $400-450 for a 15-20% cure rate. And Jublia interrupted my Super Bowl.

• Natesto: Nasal testosterone gel with the convenience of tid dosing

• Colcigel: homeopathic (really!) colchicine topical gel. Prescription only: $632 for two 15 ml bottles.

• Addyi: “Female Viagra” 10% improvement in desire/satisfaction for $800/month

• Durlaza: 24 hr extended release aspirin. 162 mg = $6

THINGS THAT MAKE ME GRUMPY

• Martin Shkreli, CEO of Turing Pharmaceuticals

• Raised price of pyrimethamine (for toxoplasmosis) from $13.50 to $750 per 25 mg tablet

• One month of maintenance therapy = $45,000

• “Supporting other R&D”
Thanks!
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Tweet questions to: @clknight

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