New Drugs for 2019

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New drugs

New tetracyclines

- Omadacycline
  - IV/PO tetracycline active against resistant gram positives including MRSA, VRE, multiple gram negatives, anaerobes; not *Pseudomonas, Proteus, Morganella, Providencia*
  - Studied in SSTI [30726689], CAP [30726692] and shown to be non-inferior to available antibiotics (linezolid, moxifloxacin)
- Eravacycline
  - IV tetracycline with slightly better gram-negative coverage than omadacycline (but still not *Pseudomonas*), BID dosing
  - Noninferior to ertapenem [27851857] & meropenem [30561562] in complicated intra-abdominal infections.
  - NOT effective for UTI
- As always, involve ID before reaching for new antibiotics.

Novel drugs for depression

- Esketamine
  - S-enantiomer of ketamine, which has been used off-label for severe depression
  - 28-day outpatient trial [31109201] of esketamine vs. placebo (in addition to oral antidepressant) in patients with treatment-resistant depression
  - Greater decrease in depression scores in treatment group—majority of effect was seen within 24 hours; significant adverse effects including dissociation
  - $1000/month
- Brexanolone
  - Progestin that acts at $GABA_A$ receptor approved for use in postpartum depression
  - 60-hour IV infusion gave small but durable reduction in depression scores at 30 days [30177236] but with significant adverse effects including sedation and loss of consciousness
  - $34,000 for one course of treatment

More new drugs for migraine

- Rimegipant
  - Oral CGRP antagonist studied for abortive treatment of migraine: 1186 patients, mean age 40, 88.7% women, 19.6% pain-free at 2h in treatment group vs 12.0% in placebo group (NNT 13). [31291516]
- Lasmiditan
  - Selective 5-HT_{1F} receptor modulator that does not cause vasoconstriction like triptans
  - More effective than placebo at relieving headache 2 hours after dosing (32% vs 15%; NNT 6) in patients with ASCVD risk factors [30446595]
- Galcenezumab for cluster headache
  - Monthly SC CGRP antagonist studied in 106 patients with frequent (17/wk!) cluster headaches; greater reduction in attacks than placebo (9/wk vs 12/wk) [31291515]

Bremelanotide for FSDD

- Melanocortin receptor agonist; mechanism unknown
- Unpublished FDA data: 1.75 mg SQ 45 minutes before sexual activity causes small (0.5/6 points) increase in desire and decrease in distress c/w placebo; no significant difference in number of satisfying events.
- High rates of adverse effects: nausea 40%, flushing 20%; 18% stopped due to adverse effects. Hyperpigmentation was rare overall (1%) but more common with frequent use and darker skin.
- $750/dose

Tafamidis for TT amyloidosis

- Transthyretin amyloidosis can cause cardiomyopathy (13% of pts with HFpEF in one study) [26224076] and has a poor prognosis
- Tafamidis stabilizes transthyretin, preventing dissociation into amyloid fibrils
- 441 patients randomized to tafamidis vs. placebo: over 30 month follow up all-cause mortality was 43% in placebo group vs 30% in treatment group (NNT 8)
- $18,000/month for daily oral therapy
- Maurer, M., Schwartz, J., Gundapaneni, B., et. al. (2018). Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. New England Journal of Medicine https://dx.doi.org/10.1056/nejmoa1805689

Voxelotor for sickle cell disease

- Direct inhibitor of HbS polymerization
- 274 patients randomized to voxeletor vs. placebo; 65% on hydroxyurea
- 51% of voxeletor group had increase in Hgb > 1.0 vs. 9% of placebo group (NNT 2) without increasing rates of vaso-occlusive crisis
- Long-term effects on morbidity/mortality unknown
- Vichinsky, E., Hoppe, C., Ataga, K., et. al. (2019). A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. New England Journal of Medicine 381(6), 509-519. https://dx.doi.org/10.1056/nejmoa1903212

Gene therapy for SMA

- Spinal muscular atrophy: autosomal recessive neuromuscular disorder with variable severity; infants with the worst form are usually on ventilator by age 2
- Onasemnogene abeparvovec is single-dose adenoviral vector that delivers SMN1 gene to neurons
- Of 36 patients treated in trials during infancy, all but three are alive without ventilation after 15-30 months of follow-up; many also have better motor function than expected
- $2.1 million/dose

Milasen for … Mila

- Batten's disease is an autosomal recessive neurodegenerative disease that presents in early childhood with seizures and progressive neurologic deficits
- Mila Makovec presented at age 6 with a novel splicing mutation that interrupted proper gene transcription
- A team at Boston Children's spent 10 months developing an antisense oligonucleotide that inhibited the mutant splicing site
- After two years of intrathecal therapy, Mila has improved but remains severely disabled
- Kim, J., Hu, C., Achkar, C., et. al. (2019). Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease New England Journal of Medicine https://dx.doi.org/10.1056/nejmoa1813279
- Kolata, G. Scientists Designed a Drug for Just One Patient. Her Name Is Mila. New York Times. Oct 15, 2019. https://nyti.ms/2AWrEa5

Drug updates

Aspirin for primary prevention

- Three recent primary prevention studies:
  - ASCEND: 15,480 adults with diabetes. 1.1% decrease in ASCVD events (NNT 100), 0.9% increase in major bleeding (NNH 100). [30146931]
  - ARRIVE: 12,546 men > 55, women > 60. Benefit not significant. 0.5% increase in "mostly mild" GI bleeding in treatment group (NNH 200). [30158069]
  - ASPREE: 19,114 adults > 70. 0.8% INCREASE in all-cause mortality in aspirin group (NNH 125). [30221595]
- Annals meta-analysis: 2.5% of women/12.1% of men may benefit from aspirin; goes up to 21.4%/40.7% if 1 CVD event = 2 major bleeds [31525775]
- Bottom line: we should be focusing on SECONDARY prevention with aspirin.

Update on SGLT2 inhibitors

- Lancet meta-analysis in type 2 DM: [30424892]
  - Modest reduction in CV events (HR 0.86) in patients with known ASCVD, no benefit in patients without.
  - Larger reduction in HF hospitalization, CV death (HR 0.71-0.79) in patients with and without history of heart failure.
  - Even larger reduction in progression of renal disease (HR 0.44-0.67) in patients with and without CKD
- DAPA-HF: 4744 patients with Class II-IV HFrEF randomized to dapagliflozin vs placebo. 2.3% reduction in all-cause mortality (NNT 43). 42% of patients had diabetes, 41% had CKD. [31535829]

Oral semaglutide for type 2 diabetes

- First oral GLP-1 agonist
- Multiple trials compared it to empagliflozin, sitagliptin, liraglutide, placebo as add-on drug to metformin
- Average A1C reduction was 1.2-1.4%, non-inferior to liraglutide (1.1%), and superior to empagliflozin (0.9%), sitagliptin (0.8%), and placebo (0.2%)
- Also promotes weight loss like other GLP-1 agonists
- $700/month

- Pratley, R., Amod, A., Hoff, S., et. al. (2019). Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. The Lancet 394(10192), 39-50. https://dx.doi.org/10.1016/s0140-6736(19)31271-1

New forms of glucagon

- Standard glucagon kit comes with powdered glucagon and a vial of saline; caregiver must mix before injection.
- *Gvoke*: pre-filled syringe that cuts 60 seconds off of administration time and makes it much more likely bystander will be able to help
- *Baqsimi*: glucagon nasal powder (no inhalation required) that is as effective as injection
- Both priced at $280 to match existing glucagon kits

Regular insulin is OK in T2DM

- Short-acting insulin analogues (lispro, aspart, glulisine) are favored by guidelines and thought to be easier for patients to time with meals but is much more expensive
- Cochrane review of 9 trials, 2519 patients: no difference in mortality, A1C or hypoglycemia with regular compared to analogue insulins [30556900]
- 2013 crossover study (100 patients, T2DM): no meaningful difference in A1C, hypoglycemia, or glucose profile if regular given with meal rather than 20-30 minutes before [23340895]
- Regular insulin: $25/10 ml; Lispro $70

Fiber for diabetes

- Viscous fiber (e.g psyllium, vegetable gums) thought to lower blood sugar via gut microbiota
- Meta-analysis of viscous fiber supplements vs. placebo/diet/fiber-free supplements in patients with type 2 diabetes:
  - 20 trials, 1353 patients: 0.58% reduction in hemoglobin A1C
  - 28 trials, 1665 patients: 14.8 mg/dL reduction in fasting glucose
- Median dose 13.1 g/d (2.5 tsp psyllium powder)
- Jovanovski, E., Khayyat, R., Zurbau, A., et. al. (2019). Should Viscous Fiber Supplements Be Considered in Diabetes Control? Results From a Systematic Review and Meta-analysis of Randomized Controlled Trials. Diabetes Care 42(5), dc181126. https://dx.doi.org/10.2337/dc18-1126

Managing mild asthma

- Standard asthma therapy steps up from SABA as needed to daily ICS
- Open-label RCT comparing albuterol as needed, daily budesonide + albuterol as needed, and budesonide/formoterol as needed in mild asthma [31112386]
  - Budesonide/formoterol PRN had lowest rates of exacerbation (20% per year vs 40% in albuterol group, NNT 5), lowest oral steroid exposure
  - Daily budesonide had better symptom control, similar exacerbation rates, higher inhaled steroid exposure
  - There is probably a group with mild intermittent asthma who would do better with ICS/LABA as a "rescue" inhaler than they would with just albuterol
- Primatene.. it's baaack!

Genotype-guided DAPT

- Ticagrelor and prasugrel have lower rates of thrombotic events than clopidogrel post-PCI but higher rates of bleeding
- Some patients have a cytochrome P450 mutation that limits clopidogrel activation—less effective for them
- RCT of 2488 patients undergoing PCI. Intervention patients had genotyping and received clopidogrel post-procedure if genotype favorable; control patients all received ticegrelor or prasugrel.
- Intervention group had 5.1% rate of composite bad outcomes including major bleeding vs 5.9% in controls (achieved non-inferiority)
- Bleeding (major & minor) occurred in 9.8% of intervention and 12.5% of control groups (NNH 37)
- Clopidogrel: $10/month; Prasugrel: $20/month; Ticagrelor: $380/month
- Claassens, D., Vos, G., Bergmeijer, T., et. al. (2019). A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. New England Journal of Medicine https://dx.doi.org/10.1056/nejmoa1907096

Oral antibiotics for osteo, endocarditis

- 1054 patients with bone/joint infection (45% prosthetic joint) randomized to IV vs oral antibiotics (specific regimen left to ID); no significant difference in outcomes after 6+ weeks of therapy [30699315]

- 400 patients with left-sided endocarditis (27% prosthetic valve) randomized to switch to oral therapy vs stay on IV after around 17 (at least 10) days of IV therapy; no significant difference in outcomes with 6 months f/u after antibiotics [30152252]
- Editorial points out that pragmatic design with multiple antibiotic regimens is useful for proof of concept, it doesn't provide guidance on a specific treatment plan [30699312]

Older patients with UTIs

- Cohort study: 157,264 English adults over 65 with diagnosis of suspected or confirmed *lower* UTI from 11/2007 to 5/2015
- 7.2% of episodes showed no antibiotic prescription and 6.2% had a delay > 24h
- Rate of:
  - Bloodstream infection: 2.9% (NNH 37) vs 2.2% (NNH 51) vs 0.2% for immediate antibiotics
  - Hospitalization: 27.0% (NNH 8) vs. 26.8% (NNH 8) vs. 14.8%
  - All-cause mortality: 5.4% (NNH 27) vs 2.8% (NNH 83) vs 1.6%
- Gharbi, M., Drysdale, J., Lishman, H., et. al. (2019). Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study BMJ 364(), l525. https://dx.doi.org/10.1136/bmj.l525

Those aren't drugs!

Inhaler training for COPD

- Meta-analysis of 8 studies (4 RCTs) with 1,812 participants over 65
- Interventions included live demo (placebo inhaler), video, written handout
- Pooled data from RCTs showed reduction in exacerbations (OR 0.71)
- Mixture of interventions and devices makes results difficult to interpret, but pharmacy teaching MDI use stands out as likely beneficial
- Study dates range from 2003-2014; unclear if results apply to dry powder inhalers
- Maricoto, T., Monteiro, L., Gama, J., et. al. (2019). Inhaler Technique Education and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease: A Meta-

Analysis Journal of the American Geriatrics Society 67(1), 57-66. https://dx.doi.org/10.1111/jgs.15602

Topical lidocaine for procedures

- RCT of 481 patients undergoing bedside procedures in the hospital
- Intervention group had 1-2 ml of lidocaine dripped onto the skin immediately before lidocaine administration (25 ga needle)
- Average procedural pain score on 100 mm VAS: 12.2 mm in intervention group, 16.6 mm in controls (p=.03)
- PICC line placement over-represented in the data set; may not extrapolate well to other procedures
- Patel, B., Wendlandt, B., Wolfe, K., et. al. (2018). Comparison of Two Lidocaine Administration Techniques on Perceived Pain from Bedside Procedures: A Randomized Clinical Trial Chest 154(4), 773-780. https://dx.doi.org/10.1016/j.chest.2018.04.018

Pharmanure

The 2019 Pharmanure List

- *Ezallor* sprinkle: Rosuvastatin sprinkles: $85/month
- *Qmiiz* ODT: Orally disintegrating meloxicam: $202/month
- *ZTlido*: 1.8% lidocaine patch for $250 more than OTC 4% patches
- *Qbrexza*: Glycopyrollate wipes for hyperhidrosis: $550/month

Opioids for dental pain in young adults

- Cohort study of 14,888 patients aged 16-25 who received opioids from a dentist c/w 29,776 matched controls; excluded those with opioid rx, “complex chronic condition”, OUD diagnosis in 12 months prior to index prescription
- Of opioid-exposed individuals:
  - 6.9% received a second prescription for an opioid 90-365 days later (vs. 0.1%)
  - 5.8% had subsequent diagnosis of OUD within the next year (vs. 0.4%)
- Correlation is not causation, but.. wow.
- Schroeder, A., Dehghan, M., Newman, T., et. al. (2019). Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and

Abuse JAMA Internal Medicine 179(2), 145-152. https://dx.doi.org/10.1001/jamainternmed.2018.5419