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In this edition:

Does the World Need Another Drug for Hot Flashes?
Fezolinetant May Fill a Niche for Some Women

Marketed as a non-hormonal option for treatment of the vasomotor symptoms (VMS) of menopause, fezolinetant (Veozah) recently gained FDA approval for treatment of moderate to severe vasomotor symptoms. Two industry sponsored, randomized trials involving 677 patients compared Veozah and placebo over 12 weeks. After the initial three-month trial, 40 additional weeks of open label use was carried out.

Results

Change in Frequency of Vasomotor Symptoms				
	Trial 1		Trial 2	
Parameter	**Veozah**	**Placebo**	**Veozah**	**Placebo**
Baseline Number of Daily VMS	10.4	10.5	11.8	11.6
Change from Baseline to Week 12	-6.4	-3.9	-7.5	-5.0

*Adapted from Veozah package insert.

- In both trials, Veozah decreased the daily number of VMS by 6.4 and 7.5 with baselines of 10.4 and 11.8.
- In the same trials, placebo decreased the daily number of VMS by 3.9 and 5.0, with baselines of 10.5 and 11.6.
- On a three-point scale, mean severity of hot flashes decreased by 0.7 points with Veozah and by 0.4 points with placebo.
- A decrease in the number of VMS was noted as early as one week and was sustained throughout the additional 40 weeks of open label use.

- Veozah was well tolerated with G.I. symptoms and headache being the most common side effects.
- Although less than 2% of patients had treatment associated elevations of liver enzymes greater than three times the upper limit of normal, the FDA recommends checking liver function studies at baseline and every three months for at least nine months.

- Looks like a fairly effective intervention. Taking a closer look at the placebo effect shows that more than half of the total effect size in lowering the number of hot flashes is related to the placebo phenomenon. It is reminiscent of the placebo effect in using SSRIs in mild depression.
- The pharmaco-economics of this drug are not favorable. It is priced at $550 a month or $18 a day or about $2.50 per hot flash avoided.

Two New Drugs in the Pipeline: Cytisinicline and Icodec

Cytisinicline for Smoking Cessation

Cytisinicline is a plant-based alkaloid that, like varenicline, binds selectively to nicotinic acetylcholine receptors. Although not yet licensed in the US, cytisinicline is used in several European countries to aid smoking cessation. In a double blind, placebo controlled, randomized trial with follow up to 24 weeks, 810 adults who smoked cigarettes daily and wanted to quit were randomized to cytisinicline 3 mg three times daily or a placebo three times daily. Results showed continuous abstinence rates were 21.1% for the active drug and 4.8% for placebo at 24 weeks. Insomnia, abnormal dreams and nausea incurred in less than 10% of each group.

Likely to be approved by the FDA, I am concerned about adherence with a TID dosing schedule.

Weekly Ultra-Long-Acting Insulin Icodec

Although icodec is not yet FDA approved, its long half-life may be a winner for some patients. In a manufacturer's sponsored study of icodec plus fast acting prandial insulin, 600 patients with type 2 diabetes (hemoglobin A1c levels, 7.0% – 10.0%) who had been taking a basal bolus insulin regimens were randomized to once weekly icodec or once daily, glargine. All patients received 2 to 4 daily doses of insulin aspart.

Results: At 26 weeks, the mean HbA1c of 8.3% had decreased to 7.1% in both groups. Time in target range and percentage achieving a hemoglobinA1c <7.0% were similar in both groups. Mild hypoglycemia was more frequent with icodec. Severe hypoglycemia occurred with similar frequency in both groups.

Offers some convenience. With the push on to lower out-of-pocket costs for diabetics, it will be interesting to see how Novo Nordisk prices this drug.

Which Kids Need Antibiotics for their Sinusitis?

There's a large overlap between symptoms of acute sinusitis and viral upper respiratory infection, suggesting that certain subgroups of children being diagnosed with acute sinusitis and subsequently treated with antibiotics derive little benefit from antibiotic use. Investigators from Children's Hospital of Pittsburgh (JAMA 2023; 330 (4):3 49–358) enrolled, 510 children ages 2 to 11 years who met the clinical practice guidelines of the American Academy of Pediatrics for acute sinusitis. These children were randomized to treatment with oral amoxicillin (80 mg per kilogram per day) and clavulanate (6.4 mg/kg/day) or placebo for 10 days. The primary outcome was symptom burden based on daily symptom scores during the 10 days after diagnosis. Secondary outcomes included treatment failure and adverse events, including clinically significant diarrhea.

Results: The mean symptom scores were significantly lower in children in the antibiotic group (9.04) compared with those in the placebo group (10.60). The length of time until symptom resolution was significantly lower for children in the antibiotic group (7.0 days) than in the placebo group (9.0 days). Children without nasopharyngeal pathogens detected did not benefit from antibiotic treatment as much as those with pathogens detected; the difference in mean symptom score was -0.88 in those without pathogens detected compared with -1.95 in those with pathogens detected. Efficacy did not differ significantly according to whether colored nasal discharge was present.

The authors cultured each of the kids at the start of treatment for M catarrhalis, H influenzae, and S pneumoniae. They later dropped the M catarrhalis pathogen, considering it colonization rather than infection. Interestingly children without S pneumoniae or H influenzae cultured comprised 53% of those enrolled.

- The authors suggest that a reasonable option to reduce antibiotic use in children with acute sinusitis would be to limit treatment to those colonized with pathogens in the nasopharynx at the time of diagnosis. In the current study population, such an approach would've resulted in a 28% reduction in antibiotic use.
- I agree that that their option seems reasonable, but not very practical. Will parents be willing to wait 48–72 hours for culture results? What about the additional costs?
- Once more, evidence that the color of snot is snot predictive of bacterial illness.

Short and Sweet

- **Lipid screening in children:** USPSTF finds insufficient evidence to recommend for or against lipid screening in children. Evidence is lacking to show that screening children or adolescents prevents later cardiovascular disease. It's an "I" recommendation.

- **Kiwi fruit for constipation:** In a study, funded by a company that markets kiwi fruit, researchers found that in patients with functional constipation and constipation-predominant irritable bowel syndrome, two peeled green kiwi fruits daily resulted in 1.5 more spontaneous bowel movements weekly compared with one bowel movement with 6 g of fiber in psyllium. Not a very moving study.

- **Sulfonylureas: more evidence for their safety.** In a study from a Scottish national registry of all patients with type 2 diabetes, researchers identified 20,000 patients who added sulfonylureas (e.g.,

glyburide, glipizide) to metformin. Their cardiovascular outcomes were compared to those of 10,000 patients who added a DPP-4 inhibitor (e.g., Januvia, Tradjenta) and 2000 who added a thiazolidinediones (e.g., Actos). During a median follow up of four years, the three groups had no significant differences in major adverse cardiovascular events. (Diabetes Care 2022 May; 46:967)

Sodium-glucose transporter-2 inhibitors (SGLT-2) and glucagon-like peptide-1 (GLP-1) are the preferred add-on therapies for patients at high cardiovascular risk. Unfortunately their costs make them unavailable to many patients. Sulfonylureas do put patients at risk for hypoglycemia and weight gain.

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