the PRUDENT prescriber

Phil Mohler, M.D.

April 2023

In this edition:

Contraception Update: Pearls from the City by the Bay

In December 2022, I attended the University of California-San Francisco conference on Controversies in Women's Health. It's an annual conference held the second week in December each year. I recommend it highly. Here are contraception pearls from Dr. E. Bimla Schwarz, MD, Professor of Medicine.

Contraception counseling:

- What proportion of US women of reproductive age experience an unintended pregnancy each year? 5% for women of any reproductive age; 10% for adolescents.
- Contraceptive counseling does **not** increase the risk for sexually transmitted infections. Contraceptive counselling does **not** reduce condom use. (Nelson HD, et al. Ann Intern Med. 2022 May)
- Listening to the patient: "Letting me say what matters to me about birth control. Taking my preferences about birth control seriously. Giving me enough information to make the best decision about my birth control method."
- "The best contraceptive for any given person is the one they want to use at this point in their life."
- Starting the conversation… "How are you feeling about pregnancy at this time in your life?"
- "Women with diabetes receive contraceptive counseling half as often as women without diabetes."

Which method?

- Thanks to the Affordable Care Act, there is now coverage without co-pay of a contraceptive in each of the 17 categories identified by the FDA.
- Since 2017, California law requires health plans to cover 12 months of self-administered hormonal contraception (pills, patch, ring, shot). In Colorado, depending on their insurance plan, patients may be eligible for up to 12 months of contraceptive being dispensed at one time.
- Dispensing less than a 12-month supply of oral contraceptives triples rates of unintended pregnancy (Judge-Golden CP JAMA Intern Med. 2019).
- "Pick a pill… ANY pill: keep it simple – generic/on their formulary – monocyclic - no need to add iron or folic acid - cyclic or continuous - START TODAY!"
- Subcutaneous Depo-Provera is better than IM: less painful, less weight gain, can be self-administered, and better adherence.
- The barriers to utilizing almost all forms of contraception are few. Check out the CDC's US Medical Eligibility Criteria, 2016.

Emergency contraception (EC):

- Dispense EC to anyone – offer IUDs to all patients – if a patient prefers oral emergency contraception, use Ella.
- "Women receiving an advance supply were more likely to take emergency contraception pills and to do so more promptly, after unprotected sex" (Rodriguez MI Contraception. 2013).
- IUDs are the most effective form of emergency contraception. The levonorgestrel 52 mg IUD (Kyleena) was found to be non-inferior to the Copper T380A IUD (NEJM 2022 141). Pregnancy occurred in 0% to 0.3% in the two groups. Five percent of both groups sought medical care within a month of IUD insertion.
- Ulipristal (Ella, prescription) ($46 per dose) is more effective in preventing pregnancy than levonorgestrel (PlanB One-step, OTC) ($11 per dose).
- With Ulipristal need to wait five days before starting hormonal contraception as it will lower ulipristal's effectiveness. If the patient wants to start hormonal contraception right away, prescribe levonorgestrel (Plan B One-Step) for emergency contraception.
- Both oral forms of EC maybe less effective for individuals with higher body weights. Ella is less effective for weights >198 pounds (BMI 30). Plan B One-step is less effective for patients whose weight is >155 pounds (BMI 25). The American Society of Emergency Contraception states that no individuals should be refused or discouraged from using emergency contraception based on their weight.
- Pregnancies after unprotected intercourse per 1000 women: Nothing, 80; Plan B One-step, 10; Ella, 5; either IUD, 1. (Raymond EG NEJM. April 2, 2015)

FDA Goes Out on a Limb Again:
Lecanemab Approved for Early Alzheimer's Disease

Background:

The amyloid hypothesis is thought to be related to the etiology of Alzheimer's Dementia (AD). However, nearly all pharmaceutical therapies targeting amyloid have failed to significantly alter the clinical course of the disease during the past two decades.

Lecanemab (Leqembi) now joins Aduhelm in enjoying the FDA's fast track approval process. As you may recall Aduhelm was lambasted by major health care systems, the Department of Veterans Affairs, congressional committees and this publication for its lack of benefits and risks of brain swelling and bleeding. Subsequently Medicare sharply limited coverage. Biogen halved its annual price to $28,800.

Studies of Lecanemab:
In a phase 2 trial of 854 patients (Alzheimer's Research & Therapy volume 13,:80 (2021), the researchers failed to show lecanemab results superior to those of placebo where the primary endpoint was a 12-month clinical change on the Alzheimer's Disease Composite Score.

The Clarity AD trial (NEJM Jan 4, 2023) included 1,795 individuals with early AD (defined as mild cognitive impairment or mild dementia due to AD) who are randomly assigned to receive intravenous lecanemab or placebo.

Clinical Results: Statistically significant differences favoring lecanemab over placebo were observed on the primary outcome, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score. The treatment benefit of 0.45 points on the 18-point CDR–SB score is well below the minimal clinically important difference in in AD clinical trials. Various dementia experts have suggested that the minimal clinically importance difference on the CDR-SB should be 1-2.5 points.

Bias/Side-effects: A common source of unblinding bias influencing the results of amyloid targeting immunotherapy trials is an event called amyloid-relating imaging abnormalities (ARIA). ARIAs necessitate additional MRI surveillance for edema and/or hemorrhage. The reported incidences of ARIA in the lecanemab and placebo groups were 12.6% and 1.7% respectively, for ARIA-Edema and 17.3% and 9.0%, respectively, for ARIA-Hemorrhage. In the small number of participants with symptomatic ARIA-Edema (2.8% of the treatment group), the most common symptoms were headache, visual disturbance and confusion.

Carriers of Apoe4: The data regarding the relative benefit of lecanemab in patients carrying or not carrying the Apoe4 genetics contradicts all the amyloid trials in which only carriers have benefited from anti-amyloid medications.

Institute for Clinical and Economic Review (ICER):
ICER is an independent, non-profit research company that produces analyses of the evidence of the effectiveness and value of drugs and other services. ICER rated lecanemab promising, but inconclusive (P/I) in providing a net health benefit over supportive care alone in patients with mild cognitive impairment due to Alzheimers Dementia or mild Alzheimers dementia. ICER calculated the health benefit price benchmark to be between $8,900-$21,500 per year. This is significantly north of pharma company Eisai's proposed annual price of $26,500. Medicare is not on board for paying for lecanemab as of March 6, 2023.

MY TAKE

What we know and don't know:

- The pathogenesis of AD is much more complex than first thought.
- What's the answer? A cocktail with an anti- amyloid drug plus an anti-inflammatory? Starting treatments before patients become symptomatic?
- All five of the monoclonal antibodies studied for treatment of AD consistently make amyloid go away. The PET scans showing the disappearance of amyloid are beautiful sights to behold. But is this "much ado about nothing?"

The Good News

- A few fewer ARIAs than with Aduhelm
- Most ARIAs cleared with stopping the drug.
- The Clarity-AD trial recruited a more diverse population than previous AD studies with 22.5% Hispanics and 4.5% Blacks.

The Bad News

- Logistically, lecanemab treatment involves IV infusions q 2 weeks, a passel of MRIs and huge medical costs- $26,500/year for the medication alone.
- Clinically, lecanemab's clinical treatment effect size is negligible as have been all the monoclonal antibodies tested for AD. I have seen no evidence to make me believe that lecanemab creates a change that is going to be noticeable in patients' lives.

The Really Sad News

The FDA persists in its blind, mindless accelerated approval of drugs that don't work for Alzheimer's disease. This is an affront to science. I am disappointed that the Alzheimer's Association continues to foster hype and false hope for its members and their families.

Looking for previous versions of the Prudent Prescriber newsletter? Good news, 10 YEARS of monthly editions are now available on rmhp.org.

Prudent Prescriber
Authored by Phil Mohler, MD

ROCKY MOUNTAIN HEALTH FOUNDATION

Sponsored by Rocky Mountain Health Foundation

United Healthcare | ROCKY MOUNTAIN HEALTH PLANS®

Distributed by Rocky Mountain Health Plans, a UnitedHealthcare Company

the PRUDENT prescriber
Phil Mohler, M.D.