the PRUDENT prescriber

Phil Mohler, M.D.

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In this edition:

Paxlovid: The Good, The Bad and The Ugly
Pfizer Wins the Pharmaceutical Outrage of the Month Award

Some facts and lots of Phil's opinions

First, recall that Paxlovid is indicated for outpatients with mild-moderate COVID-19 symptoms and must be started within five days of onset of symptoms to be effective.

The Good News: There is evidence that Paxlovid is effective in decreasing the risk of hospitalization or death in moderately or severely immunocompromised patients (NNT = 59 to prevent one hospitalization or death in 3500 mostly vaccinated patients during February 2022 to February 2023). [JAMA Netw Open 2023 Oct] Aside from some drug interactions, Paxlovid is a relatively benign medication with metallic taste and diarrhea the most common side effects.

The Bad News: Younger, vaccinated, healthy patients with mild-moderate Covid are much less likely to benefit from Paxlovid as they are at much less risk to progress to hospitalization or death. In the study quoted above, Paxlovid was not effective in decreasing hospitalizations or deaths in a group of patients who were not immunocompromised but had medical conditions that predisposed them to Covid complications (for example, severe pulmonary disease, metabolic disease, some cancers) Finally in this study, Paxlovid was not effective in a final group who consisted largely of immuncompetent older people (age> 70) with less severe medical conditions.

Pfizer's TV ads are disingenuous. They feature a Rubenesque young woman who indicates obesity is a risk factor for severe Covid disease and an indication for Paxlovid. That criterion would wrap up a sizeable population of Americans but would not be on my long list of solo indications. Their current ad is populated by a bunch of actors who won't be eligible for AARP for another couple decades. My daughter-in-law, an internist/geriatrician, the smartest physician that I know, feels that there is absolutely no current indication for this drug.

The Ugly News: Pfizer, the manufacturer of Paxlovid announced recently that the price of a five-day course of the medication will be $1390. That's up from the $530 that Pfizer has been charging the federal government for the medication. Pfizer noted that this price "does not necessarily reflect the price a patient will pay" and said it's working to secure health insurance arrangements that would come with low out-of-pocket cost to patients. I'm skeptical. Paxlovid will continue to be free for patients through government purchases until the end of 2023.

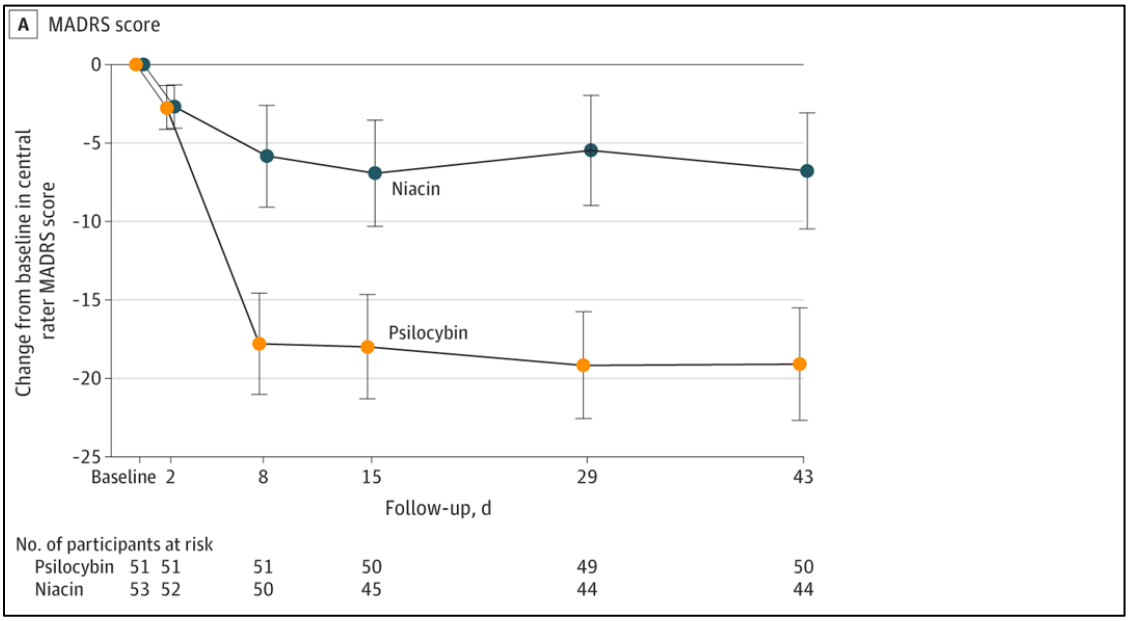
Pfizer also raised their COVID-19 vaccine price in the transition from a government benefit to a commercial market with a fourfold increase to $115-$130 per dose. Pfizer was given billions of dollars upfront during Operation Warp Speed to develop the first Covid vaccines. Their costs to produce both Paxlovid and their Covid vaccine are modest.

Psilocybin in Depression
A New Era in Psychotropic Drugs?

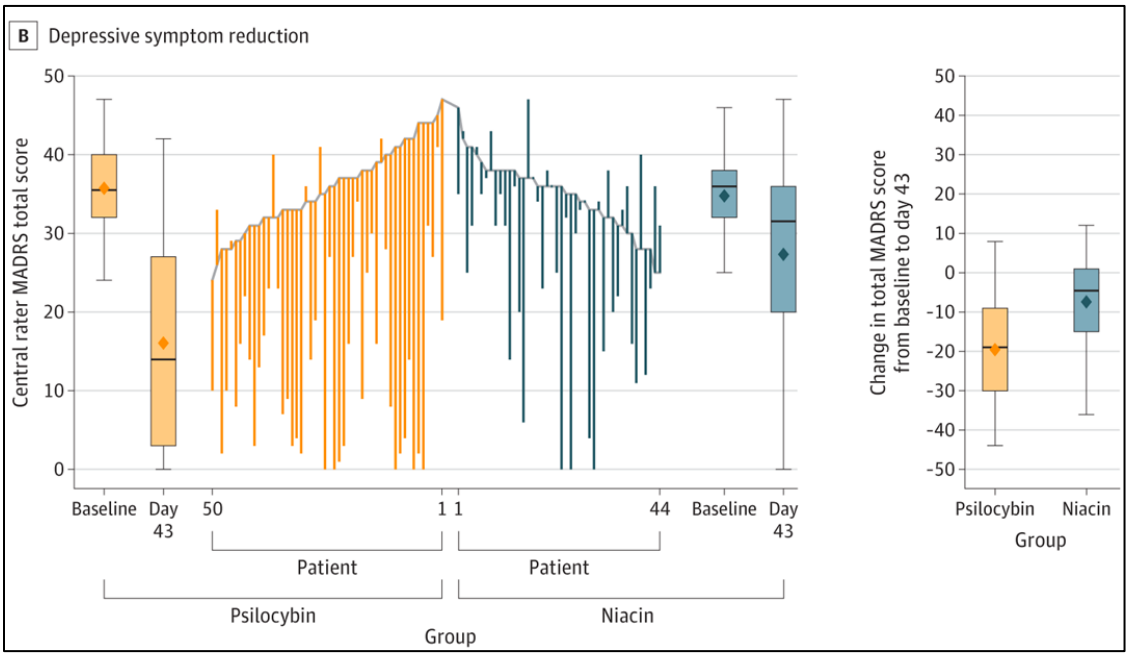
In a new, small, well designed randomized, placebo controlled, six-week trial in 104 adults, a single 25 mg dose of psilocybin administered with psychological support was associated with a rapid and sustained antidepressant effect. Psilocybin use was associated with a significant decrease in depression symptom scores compared with active placebo. No serious treatment adverse effects occurred. (JAMA Aug 3, 2023)

The study randomized 104 adults aged 21 to 65 years with a diagnosis of major depressive disorder of at least 60 days duration with moderate or greater symptom severity to 25 mg of synthetic psilocybin or a placebo, a 100 mg dose of niacin.

The primary outcome was `a change In Montgomery-Asberg Depression Rating Scale (MADRS) score (range, 0-60; higher scores indicate more severe depression) from baseline to day 43.



Adapted from Raison et al JAMA Aug 3, 2023



Adapted from Raison et al JAMA Aug 3, 2023

The "A" portion of the graph above demonstrates the rapid onset of the psilocybin anti-depressant effect by day 8 and its persistence for at least 6 weeks. Psilocybin use was associated with a significant decrease in depression symptom scores compared with active placebo (-12.3). The literature suggests a minimally important placebo adjusted decline of- 6 as clinically meaningful, while a change of -12 is considered clinically substantial. The "B" portion of the graph highlights the individual patients' responses to both psilocybin, as well as the niacin placebo.

More participants receiving psilocybin than niacin had a sustained depressive symptom response (20/48 [42%] vs 5/44 [11%]; (NNT =3.2)

Solicited adverse events (AEs) were reported by 76% of those receiving psilocybin versus 30% of those receiving niacin. The majority of solicited events were mild-- 80% in the psilocybin group and 96% in the

niacin group. Severe solicited events were reported by 3 participants receiving psilocybin (two headaches and one visual perceptual effect), and one headache was reported in the participant receiving niacin. The most commonly solicited adverse event was headache in 33 of 50 participants (66%) receiving psilocybin and 13 of 54 participants (24%) receiving niacin.

- There are significant limitations of this study: small "n", relatively short follow up, potential unblinding because of psilocybin's known psychoactive symptoms, and lack of ethnic diversity.
- None-the-less, this study adds hope to the existing literature that psilocybin may offer promise to the treatment of major depression. The appeal of a single oral dose antidepressant that has onset within a week is mind-boggling.

STIs on the Rise in the US
Doxycycline Helpful in Post-exposure Prophylaxis in High-Risk Cohorts

In a study conducted in San Francisco and Seattle, 554 men who have sex with men (MSM) and transgender women (TGW) were randomized to 200 mg doxycycline within 72 hours of condomless sex or no doxycycline with follow-up STI testing. Three hundred and sixty of the patients were HIV uninfected on pre-exposure prophylaxis (PEP) and 194 were patients with MSM or TGW living with HIV.

Results: The study primary endpoint was the number of patients who went on to develop a bacterial STI (gonorrhea, chlamydia or syphilis).

	Doxy arm N = 374	Control arm N = 180
Gonorrhea	20 (8.1%)	65 (19.8%)
Chlamydia	19 (2.5%)	39 (11.9%)
Syphilis	49(1.9%)	7 (2.1%)

Adapted from NEJM April 2023

These data suggest that the number needed to treat (NNT) to prevent one case of gonorrhea or chlamydia in this cohort was 8–10. The NNT to prevent one case of syphilis was 500. The researchers did find a slight increase in the number of gonorrhea infections with doxycycline class resistance in the doxy PEP group, compared with the standard care group. The San Francisco Department of Public Health released doxy PEP guidance in October 2022. Seattle and King County in Washington state have also released guidelines on the use of doxy PEP to prevent bacterial STI's in men and transgender people who have sex with men. In the meantime, while Rome burns, the CDC is working on formal clinical guidelines…. The National Coalition of STI Directors report that an increasing number of doctors are providing their patients with doxycycline as STI PEP including many STI clinics.

- Doxycycline is cheap and remains effective against bacterial STIs. It has become the back-up drug for treatment of syphilis in the face of the LA-Bicillin shortage.
- Broadening the use of doxy PEP to patients with lower risks of experiencing STIs could well result in increasing doxycycline resistance and markedly increasing NNTs.

Nocebo Effect
Knowing Too Much can give you Erectile Dysfunction

And finally in preparing a presentation on the placebo effect, I found this fascinating study that points out the issues of the placebo effect's evil twin, the nocebo effect.

Silvestri in the European Heart Journal, 203; 24,1928-1932 offers a stimulating study, "Knowing Too Much can give you Erectile Dysfunction (ED)."

Methods:

- 96 men (average age 53), all newly diagnosed with either hypertension or angina were started on atenolol 50 mg per day. All denied ED.
    - Group 1 (32 patients) did not know the drug they were taking.

- Group 2 (32 patients) were told the drug they were taking, but not the side effects with respect to ED.
- Group 3 (32 patients) were told that the drug had ED side effects ("It may cause ED, but it is uncommon.")

- After 90 days, the patients were asked if they had experienced erectile dysfunction.
- Those patients reporting ED were then randomized to Viagra 50 mg or placebo for at least three different "attempts" in the next week.
- Finally, these patients were again queried regarding their sexual performance.

Results:

- Group 1 (did not know the drug) had 3.1% ED (1 patient).
- Group 2 (knew the drug but not the ED side effects had 15.6% ED (5 patients).
- Group 3 (new drug and ED side effects) at 31.2% ED (10 patients).

In patients reporting ED after atenolol, Viagra and placebo were equally effective in reversing ED – they both worked 100% of the time.

MY TAKE

- Men's reporting of their sexual prowess in the locker room and in clinical studies is suspect.
- Research reveals that 24%–26% of patients respond to a placebo with a negative effect (nocebo).
- There's a Nobel prize in the works for the clinician who sorts out tempering appropriate disclosure about a newly prescribed drug while minimizing the nocebo effect.

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Authored by Phil Mohler, MD

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