# the PRUDENT prescriber

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## Comparative Clinical Effectiveness Is ICER the Answer?

The Institute for Clinical and Economic Review (ICER) was founded in 2006 by Dr. Stephen Pearson at Massachusetts General Hospital. This organization's home page declares: "The US health system is distinctly innovative but fails to provide high-value care to all patients at a price they and the nation can afford." Here's a synopsis of ICER's recent evaluation of Covid-19 outpatient drugs for patients with mild to moderate illness. They compared sotrovimab, molnupiravir, Paxlovid, and fluvoxamine in their effectiveness in preventing hospitalization/death in outpatients with mild to moderate Covid-19.
Results:

| Hospitalization or Death from any Cause | | | |
|---|---|---|---|
| **Trial** | **Intervention** | **Placebo** | **NNT (Number Needed to Treat)** |

| | | | |
|---|---|---|---|
| Sotrovimab | 6/528 (1.1%) | 30/529 (5.8%) | 21 |
| Molnupiravir | 48/709 (6.8%) | 68/699 (9.7%) | 36 |
| Paxlovid | 8/1039 (0.8%) | 66/146 (6.3%) | 18 |
| Fluvoxamine | 79/741 (11%) | 119/756 (16%) | 20 |

* NNT is Number Needed to Treat to prevent one additional hospitalization or death

| Base-Case Incremental Cost Effectiveness Ratios | | | |
|---|---|---|---|
| **Treatment** | **Comparator** | **Cost per QALY* Gained** | **Cost per Hospital Stay Averted** |
| Sotrovimab | Usual care | $69,000 | $91,000 |
| Molnupiravir | Usual care | $55,000 | $63,000 |
| Paxlovid | Usual care | $18,000 | $21,000 |
| Fluvoxamine | Usual care | $6,000 | $7,000 |

* QALY is quality-adjusted life years - see www.icer.org for more information

ICER Concludes: "And at their current negotiated price (sotrovimab, molnupiravir, and Paxlovid) or their generic market price (fluvoxamine), ***these drugs appear—at this time—to have prices reasonably aligned with patient benefits.***"

## MY TAKE

- Take this as an example of ICER's work. In the face of the fact that the clinical studies for all four drugs were done prior to Omicron, I'm not certain that these data are practically useful in March 2022. Nonetheless you get the gist of ICER's goals:

- Is the new product more effective than the older one?
- What's a fair price for the new product, based on patients' perspectives of what is important to them?
- How do you translate the evidence into insurance coverage that insures the best patient outcomes?

Comparative clinical effectiveness is a critical tool in assuring fairly priced drugs available to all. Is ICER the tool? I hope so. Yet ICER's claims of "free from financial conflicts of interest" while interfacing with Big Pharma, the FDA and the health insurance industry stress my Healthy Skepticism.

## Avoid these Five Low Value Clinical Interventions

### 1. Tyrvaya – a BID nasal spray of varenicline (yep Chantix) for dry eyes.

Claiming that it activates the trigeminal parasympathetic pathways in the nose and therein increasing tears, Oyster Point Pharmaceuticals brought this product to market with filter paper Schrimer's scores.

The confirmatory clinical trials (Onset 1 and Onset 2), Tyrvaya showed NNTs of 3 and 5 to increase the Schrimer score distance by at least 10mm. There were no "Try this and see if it makes your eyes better" clinical trials. They did report 82% of the Schrimer test participants sneezed. At $600 a month for Tyrvaya, consider OTC lubricants ($10-$15/month) or generic Restasis (cyclosporine) available at $178. (GoodRx, March 2022)

### 2. Loreev XR- an extended-release version of lorazepam.

Available as once a day as 1 mg, 2 mg, and 3 mg extended-release capsules, this is a potential convenience drug for the niche patient who is on a stable, evenly divide dose (usually TID) of lorazepam and can't remember to take multiple doses. Not for initial treatment. Black box like all benzos. Both Loreev XR and immediate acting lorazepam are flat priced for all doses. A month's worth of the shorter acting lorazepam will cost you $13, while you will need to shell out 22X that ($285) for Loreev XR. I'll set a reminder on my phone for that kind of savings.

### 3. Adding a muscle relaxant to ibuprofen in non-radicular back pain.

This was a double-blinded randomized controlled trial study conducted in two

ERs in 320 patients who presented with acute (average duration 72 hours) non-radicular back pain. They were all given 600mg of ibuprofen to be taken up to three times a day. They were then randomized to receive placebo, baclofen 10mg, metaxalone 400 mg (Skelaxin) or tizanidine 2mg (Zanaflex) and were instructed to take 1-2 capsules up to 3 times a day. One week later the participants were queried. All groups improved compared to baseline. Adding a muscle relaxant to ibuprofen did not improve functional outcomes or pain or lessen the number of participants reporting moderate to severe back pain.

MY TAKE

I'm guilty of confirmation bias in including this study. I am of the firm opinion that any positive effects of muscle relaxants on pain are related to their soporific side effects. (Ann Emerg Med 2019; (74);512-520). Cashin et al. (BMJ 2021 July 7; 374) in a systematic review and meta-analysis of 49 trials looking at the efficacy and safety of muscle relaxants for non-specific back pain concluded: non-benzo muscle relaxants increase the risk of adverse events and provide "small but not clinically important reductions in pain intensity."

*And not meds, but important procedures to avoid….*

### 4. Unnecessary bimanual exams and pap smears in young women

The National Family Growth Survey (JAMA Intern Med 2020 Jan 6) assessed the prevalence of bimanual pelvic exams (BPEs) and pap smears in adolescent women ages 15-20. Of 3140 respondents, 23% received BPEs and 19% received pap smears in the previous year. The authors considered 72% of the pap smears and 54% of the BPEs to be potentially unnecessary (performed as part of routine exams in patients who were not pregnant, not using IUDs and not treated for sexually transmitted infections in the past year). Recall that a prescription for birth control pills is not an indication for a bimanual exam or a pap smear. My Take: It is time to make inexpensive oral contraceptives over the counter in the USA as they are in much of the world.

### 5. Platelet-rich plasma does not improve knee arthritis.

This Australian triple blinded study (avg. age 62, 59% women) involved 3 intra-articular injections at weekly intervals of either platelet-rich plasma or saline (JAMA. 2021; 326(20): 2021-2030). The trial included 288 adults aged 50 years or older with mild to moderate radiographic knee osteoarthritis, treatment with platelet-rich plasma vs placebo injection resulted in a mean change in knee pain scores of −2.1 vs −1.8 on an 11-point scale (range, 0-10) and a mean change in medial tibial cartilage volume of −1.4% vs −1.2% at 12 months. Neither comparison was statistically significant.

## Sprint Trial Follow-up

The much-ballyhooed Sprint Trial published in November 2015 encouraged aggressive blood pressure lowering in hypertensive persons who were at increased risk for cardiovascular disease. In the May 20, 2021 NEJM, the SPRINT Research Group released follow-up (3.3 years) data from this randomized controlled trial (RCT) of 9361 patients who were randomized to intensive BP treatment (target systolic BP < 120 mmHg) or standard treatment (target systolic BP < 140 mm Hg).

Results:

| Outcomes | Intensive Cohort N = 4678 | Standard Cohort N = 4683 | NNT (Number Needed to Treat) |
|---|---|---|---|
| Composite of MI, stroke, heart failure and death from CV causes. % per year | 1.77% | 2.40% | 160 |
| All cause mortality % per year | 1.06% | 1.41% | 286 |

Adapted from Final Report of Trial of Intensive vs Standard Blood Pressure Control NEJM May 20, 2021

Emergency Visits or Serious Adverse Events

| Outcomes | Intensive Cohort N = 4678 | Standard Cohort N = 4683 | NNT (Number Needed to Treat) |
|---|---|---|---|
| Hypotension | 1.77% | 2.40% | 160 |
| Syncope | 1.06% | 1.41% | 286 |
| Acute kidney injury/ARF | 201 (4.0%) | 120 (2.6%) | 71 |
| Serum Na <130 mmol/L | 189 (4.0%) | 103 (2.2%) | 36 |
| Serum K <3.0 mmol/L | 117 (2.5%) | 75 (1.6%) | 111 |

Adapted from Final Report of Trial of Intensive vs Standard Blood Pressure Control NEJM May 20, 2021

## MY TAKE

- After 39 months of follow-up, the authors of this large, well-designed, randomized controlled trial again tout aggressive hypertensive treatment in this group who were at high risk for CV complications. As is their wont, they report relative risk reductions, hazard ratios and p values with lots of zeroes. I calculated the more clinically useful absolute risk reductions and Numbers Needed to Treat.

- AAAARRRGGGGHHH. To my mind, this is magical thinking on the authors' part. The Number Needed to Treat (NNT) with more aggressive BP control for one year is 160 to prevent one MI, stroke, acute episode of CHF or death from a CV cause. The NNT to prevent one death from all causes is 286. Those are small size effects and suggest limited practical application.

- Then take a look at the adverse events associated with aggressive therapy. The Numbers Needed to Harm (NNH) are much smaller than the

NNTs. Hypotension and syncope occurred every 71 and 91 patients, respectively in those patients treated with the more aggressive therapy.

- Don't SPRINT, Crawl! For most hypertensive patients at high risk for a CV event, the aggressive goal of a systolic BP of 120 mm Hg or less is not prudent!

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