

Why worthless drugs sometimes seem to work — What we can learn from the FDA's withdrawal of the decongestant phenylephrine

Last month, some of the most iconic over-the-counter name brand medicines took a hit. The FDA's [Nonprescription Drug Advisory Committee](#) (NDAC) unanimously voted that phenylephrine, the nation's most popular oral nasal decongestant, is [not effective in tablet form](#).

Used for the temporary relief of stuffy nose, sinus, and ear symptoms caused by the common cold, flu, and allergies, phenylephrine is the active ingredient in Sudafed PE and some versions of Mucinex, Dayquil, Tylenol Sinus, and Advil Sinus Congestion, as well as store brands based on the same formulations. Considering that individuals in the United States are estimated to suffer from more than [one billion colds](#) every year, and a sizable most of them oral pill or another, the decision will upend the cold therapy market.

Phenylephrine has been approved by the Food and Drug Administration for more than 45 years. In 2006, it became the main ingredient in over-the-counter decongestants after an FDA law required pseudoephedrine, an even older approved ingredient, to be moved behind counters because it could be illegally processed into methamphetamine.

The original Sudafed tablet with pseudoephedrine [remains available](#) behind-the-counter with the "PE" designation. Also an ingredient in nasal sprays to treat congestion, phenylephrine will not have to be removed from these formulations.

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Behind the re-review

The vote was inevitable in view of the findings of a [briefing document](#) prepared for the committee by the FDA. It found that the oral bioavailability (the extent to which a medication can be used by the body) of the drug is less than 1%, not the 38% often cited in the literature. A half century ago, the FDA set different, more stringent, breathing standards than today.

The review also found that the original studies that purportedly supported the efficacy of phenylephrine contained methodological, statistical, and data integrity flaws. According to the [Yale School of Medicine](#), "six of the seven studies considered in the 1970s were submitted by Sterling-Winthrop, one of phenylephrine's manufacturers, which may have played a role in influencing the original panel's decision."

Moreover, the drug is not without significant [side effects](#), including mild upset stomach, trouble sleeping, dizziness, lightheadedness, headache, nervousness, shaking, and rapid heartbeat. At higher doses, it can increase blood pressure.



Credit: Mike Mozart/Flickr (CC BY 2.0)

The NDAC verdict is a blockbuster finding because of the popularity of phenylephrine-containing products. According to the FDA briefing document, *242 million packages or bottles* of phenylephrine products were sold in 2022, which resulted in \$1.76 billion in sales.

Presumably, many of those purchases were by repeat users who thought that the products offered relief from their symptoms, so what's going on here?

Placebo effect?

There are two phenomena that are well-known by physicians that can explain this.

The first is the placebo effect, the ability of an inactive treatment, such as the proverbial “sugar pill,” to alleviate a pain or a sign or symptom of illness. A placebo can induce measurable physiological changes like those observed in subjects taking effective medications. Physical signs that have been shown to improve after “treatment” with a placebo include changes in [blood pressure, heart rate, and even various blood test results](#). Symptoms especially amenable to improvement with a placebo include pain management, stress-related insomnia, and fatigue and nausea from cancer treatment.

Thus, the theory would be that you take a phenylephrine pill which is little more than a placebo, and the illusion of taking an effective medicine makes you believe your symptoms improved. Scientists believe that goes on with other, popular pain-relieving medicines.

A [2020 review published in BMJ](#) that examined data from more than 140,000 patients with various chronic pain conditions found placebo responses could account for as much as 75 percent of the benefits of even effective drugs.

Post hoc, ergo propter hoc fallacy?

The second possible explanation has a more complicated name but is a simple phenomenon. It’s called the *post hoc, ergo propter hoc* (after this, therefore because of this) fallacy, which mistakenly links two events as cause and effect because one happens after the other.

Let us posit, as the FDA and its advisory committee did, that phenylephrine in pill form is inactive, yet many patients with congestion still take it several times a day for a couple of days. Many of them say they feel better. Inasmuch as it’s used to treat symptoms caused by illnesses like colds, flu, and allergies that resolve on their own without treatment, it’s not surprising that people think, “I took the drug and felt better. The drug worked.”

There is another phenomenon that is another manifestation of the *post hoc, ergo propter hoc* fallacy: believing, falsely, that there was a bad outcome from a drug. I had a personal near-example of it many years ago. I was a medical resident at a major cancer center. As part of a treatment protocol, I was charged with giving a 4 a.m. intravenous dose of an experimental drug. I was groggy from sleep and had trouble getting all the bubbles out of the syringe. So, there I was, flicking and tapping to get the last bubble out before injecting it, when the patient expired — just stopped breathing and died. (There was a “do not resuscitate” order, so that was that.) It was 4:01 a.m.

If I had administered the drug exactly on time, the patient would have died within seconds of receiving it, and the investigators on the protocol, the maker of the drug, federal regulators and I would all have assumed, incorrectly, that the drug was the cause of death.

There is a saying in medical research that the plural of anecdote is not data — in other words, a single example should never be used to extrapolate a broader rule about, well, anything

That is why we do (or should do!) rigorous clinical trials to test the safety and efficacy of new drugs and other interventions. Had such studies been done properly in the first place with phenylephrine, Americans would have avoided a few side effects and saved lots of money.

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