Negative Studies Are Usually Right: Vetting the Pseudoaxioms

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I recall the day a woman from the Office of Physician Misconduct explained to our faculty what it means to be cited by the state. Like police in the rearview mirror, her presence rattled me. When asked for an example, she was swift and certain, recounting a tale of ketamine administration in a head-injured patient. The physician involved lost his license.

Reversals of conventional medical wisdom are common,[1,2] a fact cemented by Prasad et al[2] in a landmark 2013 article and memorialized by Sidney Burwell, who mused that half of what medical students are taught will, within 10 years, be revealed as wrong.[3] The danger of ketamine in head injury, for instance, has been recently and elegantly deconstructed: there is none.[4,5]

Physicians agree almost universally on the veracity of Burwell's dictum, though perhaps only in theory. In reality everyone wants change but nobody likes it. For physicians, whose authority is derived in large part from heirloom knowledge and experience, collected wisdom is the foundation of our expertise. Reversals challenge the core of medical authority and personal accomplishment by suggesting expertise is not just impermanent but also often false. Medicine humbles.

In this issue of *Annals*, we are humbled again by Claveau et al,[6] who offer a study challenging the age-old teaching that acute afterload reduction in the setting of aortic stenosis is perilous. Although limited by observational design, the report is nonetheless more valid and reproducible than any relevant data set of which I am aware. Virtually all assertions I could find suggesting danger with nitroglycerin in the setting of aortic stenosis were either physiologic or unreferenced.

I have routinely taught trainees to be wary of aortic stenosis in acute pulmonary edema. Despite being slightly esoteric (or perhaps because of it), the teaching has been a staple of my bedside arsenal. I recall the certainty and foreboding tone of those who taught me the axiom—and I recall never having researched it myself. I will henceforth recall my surprise at being recently unable to locate any sustainable evidence to support it.

The study raises an important question about the nature of evidence hierarchies and of actionable evidence: can a chart review study unveil a pseudoaxiom,[7] reversing common teaching and practice? The answer, as is so often the case in medicine, is it depends. In this case, I believe the investigators' conclusions are likely to be accurate for 3 reasons.

First, their bias-reduction methods were rigorous[8] and their endpoints wisely chosen. Hypotension, mortality, and vasopressor use are objective and typically well documented, making them strong variables for chart review.

Second, the investigators selected patients with established, severe aortic stenosis being treated for acute pulmonary edema, precisely the group traditional teaching suggests to be at maximum risk from nitrate administration.

Third, the results are negative. The absence of association between important hypotension and nitroglycerin is difficult to explain unless the drug poses either no danger or rare danger. Although observational designs commonly lead to dubious findings, these are typically based on tenuous endpoints, poor patient selection, or confounding. The first 2 biases are well minimized here, and although confounding tends to be rampant when associations are found, *it is an unlikely explanation for the absence of associations.* The only way for confounding to neutralize (ie, "zero out") a cause-and-effect relationship is for discordant confounding variables to have an effect both directionally opposite and perfectly equal to the combined effect of the causal agent and all concordant confounders.

Said another way, if the true effect of nitroglycerin in the present study was, for instance, a 20% increase in dangerous hypotension among aortic stenosis patients, that effect must have been masked. This would require a complex interplay of dozens of characteristics converging to form an aggregate confounding effect that was identical and opposite to the 20% effect: these multiple unrecognized characteristics of the groups would have to have led to

either precisely 20% more hypotension among patients in the control groups or precisely 20% less among those with severe aortic stenosis. Either circumstance (or some perfect combination of both) would conceal the 20% effect of nitroglycerin. Such a coincidence stretches the bounds of credulity.

Moreover, because unrecognized confounders are ubiquitous, when mathematical associations between variables are discovered in observational studies they are much more likely to be due to one or more of these confounders than to any single causal relationship. This simple, Bayesian reality (the likelihood of confounders causing spurious associations is far higher than the likelihood of confounders converging to match and oppose a single causal effect) is why well-performed observational studies finding no association are often correct, whereas those reporting associations are often not.

This is, moreover, consistent with what is known of today's scientific corpus. Ioannidis[9] famously proved that most research findings are false, partly based on probability. Simply put, too many published research findings are positive in comparison to the likelihood of a positive finding. To make matters worse, virtually all incentives align with researchers finding a positive result: prominent journals are more likely to publish positive findings, grants are more likely for those publishing in such journals, and for-profit interests seek favorable positive findings. Conversely, negative findings are less interesting to readers, less likely to effect change, and less likely to be published.

What, then, should we take away from the nifty chart review by Claveau et al?[6] When it comes to nitrates and aortic stenosis, as with any intervention, only a large, high-quality, randomized trial can more definitively untangle the effect of afterload reduction. In the meantime, however, no practitioner using nitroglycerin in the setting of aortic stenosis can be reasonably faulted for untoward outcomes. Nitroglycerin remains a mainstay in the treatment of nonhypotensive clinical acute heart failure syndromes, and the current study—the best and only modern examination—offers no reason to adjust this standard for patients with aortic stenosis.

Medical reversals are the parables of modern medicine; there is always a moral. In this case, it is probabilistic. Although observational data may trump untested theories, beware the observational study that finds associations—and embrace the one that does not.

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REFERENCES

1. Prasad V, Cifu A, Ioannidis JP. Reversals of established medical practices: evidence to abandon ship. *JAMA*. 2012;307:37-38.
2. Prasad V, Vandross A, Toomey C, et al. A decade of reversal: an analysis of 146 contradicted medical practices. *Mayo Clin Proc*. 2013;88:790-798.
3. Pickering GW. The purpose of medical education. *Br Med J*. 1956;2:113-116.
4. Cohen L, Athaide V, Wickham ME, et al. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. *Ann Emerg Med*. 2015;65:43-51.
5. Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: no contraindication except hydrocephalus. *Ann Emerg Med*. 2015;65:52-54.
6. Claveau D, Piha-Gossack A, Friedland SN, et al. Complications Associated With Nitrate Use in Patients Presenting With Acute Pulmonary Edema and Concomitant Moderate or Severe Aortic Stenosis. *Ann Emerg Med*. 2015;66:355-362.
7. Newman DH. Truth, and epinephrine, at our fingertips: unveiling the pseudoaxioms. *Ann Emerg Med*. 2007;50:476-477.
8. Gilbert EH, Lowenstein SR, Koziol-McLain J, et al. Chart reviews in emergency medicine research: where are the methods? *Ann Emerg Med*. 1996;27:305-308.
9. Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2:e124.