

Why were the benefits of tPA exaggerated?

The role of interpretation bias

Griffin Trotter

Assistant professor
St Louis University
Center for Health Care
Ethics and Emergency
Medicine Division
Salus Center (Health
Sciences)
3545 Lafayette Ave
St Louis, MO 63104

trotterc@slu.edu

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News magazine *US News and World Report* began an article about thrombolytic treatment of acute stroke with the following anecdote:

One Wednesday morning in January, 36-year-old Laurie Lucas was rushing about, dressing her daughters for school and talking on the phone, when a strange confusion swept over her. She felt woozy. Her right arm flailed about and her right leg went weak. Paramedics arriving at Lucas's Sanford, Florida, home thought she was having epileptic seizures, but brain scans revealed a blockage of an artery that supplies the brain with blood. Lucas, a physically fit former professional cheerleader, had suffered

a massive stroke . . . If Lucas had been stricken a year ago, before a new treatment was developed, she almost certainly would have died.^{1(p62)}

This story is interesting but misleading. It is not plausible that physicians could accurately conclude that Laurie Lucas “almost certainly would have died” without treatment. Nor is it true that “massive” strokes are likely to benefit from thrombolytic treatment.² In addition to several anecdotes, the *US News and World Report* article includes “expert” testimony in which prominent physicians exaggerate the efficacy and effectiveness of the new treatment.

Summary points

- Interpretation bias occurs when there are systematic distortions in the interpretation of data from scientific studies
- Interpretation bias may lead to errors in clinical judgment and to unrealistic patient expectations
- One source of interpretation bias is the “fallacy of selective emphasis,” which occurs when commentators focus intensely on a narrow point of interest and overemphasize its importance
- The establishment of a division of labor between clinician-researchers and clinician-interpreters might help to ameliorate the fallacy of selective emphasis
- Steps to address the fallacy of selective emphasis should be coordinated with other efforts to reduce interpretation bias

Such exaggerations also appear in medical journals and other professional venues. Specialists have announced “the decade of the brain,”³ a “new era of proactive rather than reactive stroke therapy,”⁴ and “transformation from a realm of fatalism to a field of therapeutic opportunities.”⁵ Landis and associates write, “With the tools in hand, recognition of ischemic stroke as a medical emergency and application of prudent thrombolytic techniques will have a major impact on stroke morbidity and mortality.”⁶(p226) Some commentators even warn of lawsuits if thrombolytic agents are not given to eligible stroke patients.⁷ These claims are without scientific basis.⁸⁻¹⁰ Yet, robust exaggerations and effusive sentiments of this sort appear not merely in the literature concerning acute stroke but on other topics as well. They are a serious problem because they exhibit interpretation bias, which may lead to errors in clinical judgment and to unrealistic patient expectations.¹¹

SOURCES OF INTERPRETATION BIAS

Interpretation bias occurs when systematic distortions arise in the interpretation of data from scientific studies. Ideally, interpretation bias would be eliminated directly at the clinical level. Each physician would be an expert at interpreting scientific data and would have unlimited time to review the medical literature. Indeed, some progress has been made toward this ideal with the emergence of evidence-based medicine. Still, given the astounding volume of medical data and the complexities of statistical analysis, most clinicians need help to integrate the available information into justifiable clinical strategies.¹²

Interpretation bias usually occurs at intermediary stages, as data sift their way through various medical and nonmedical interpreters on their way to clinicians and patients. At least two forces outside the medical profession pertain. First is the need for the news and entertainment

industry to discover interesting and important events. Second is the imperative of drug and device manufacturers to sell their products.

In media coverage of health research, the tendency is to focus on dramatic urgent interventions and to highlight the most startling or momentous claims about possible medical benefits. Inaccurate or stilted reporting frequently follows, often with powerful effects on patient and clinician perceptions.^{13,14} Media demands or pressure from political support groups may produce a feeling of urgency among medical researchers to announce something memorable and important.¹²

Drug and device manufacturers target individual clinicians and patients with advertisements, gifts, and grants.¹⁵ Although many clinicians maintain that their practice patterns are unaffected by propaganda from pharmaceutical corporations, the companies themselves clearly believe differently.¹⁶ Sponsorship plays an important role in cultivating expectation bias, “bandwagon bias,” and protreatment bias.¹² Expectation bias can occur when companies aggressively hype their products before the products are actually tested. Subsequently, medical researchers and interpreters may exhibit bias in finding what they expect to find. Bandwagon bias, which is closely related, occurs when companies enlist a critical mass of support for their products. As McCormack and Greenhalgh note, an unstated presupposition seems to be that “if enough people say it, it becomes true.”¹² Finally, drug and device manufacturers benefit from an implicit protreatment bias. When few proven or well-publicized alternatives are available, clinicians and patients will use their products even when little or no data exist that demonstrate clinical benefits.

The deleterious influence of corporate sponsorship has led to a review of researchers’ financial conflicts of interest.^{17,18} Medical journals and other reputable sources of clinical interpretation now frequently require authors’ disclosure of possible financial conflicts of interest.¹⁹ Whether such measures are sufficient to counterbalance bias remains a topic for debate. To eradicate corrupting influences, it may be tempting to sever altogether the relationship between medical inquiry and for-profit industry. However, such measures would threaten the vitality of clinical research by undermining resources.

FALLACY OF SELECTIVE EMPHASIS

Perhaps the focus on financial conflicts of interest has diverted attention from another source of bias in clinical interpretation: the fallacy of selective emphasis. This fallacy (originally described by philosopher John Dewey) occurs when intense focus on a narrow topic of interest manifests itself in an unintentional but systematic exaggeration of the importance of the particular point of interest.²⁰(pp31-41) In epidemiologic parlance, we

might equate this fallacy with “preoccupation” bias. When people spend much time and energy scrutinizing something, they often assume that the object of scrutiny must be important. Two important sources of the fallacy of selective emphasis seem to apply when medical researchers interpret their own work or related work in their field.

First, most researchers are “superspecialists”—that is, medical specialists with particular research interests that occupy a large proportion of their time and energy. Because of their narrow focus, superspecialists may be prone to develop partially skewed medical worldviews. But accurate interpretation requires someone who can estimate the effects of new ideas within a wide range of clinical scenarios and who is adroit at considering a gamut of competing possibilities. A competent generalist, specially qualified in interpretive methods and thoroughly familiar with the pertinent literature, seems best for this role.

Second, researchers have a natural interest in promoting their chosen specialties and areas of research. This interest is not merely a matter of money and greed but may involve the enhancement of prestige, professional self-image, and the sense of a personal calling. Researchers would not choose their specialties if they did not think that they were interesting, promising, and important.

These sources of optimism are a credit for the medical researcher but a liability for anyone with the task of interpreting the medical literature—especially for those involved in deciphering the effects of their own work.

TOWARD EFFECTIVE CLINICAL INTERPRETATION

McCormack and Greenhalgh have suggested that journal editors “encourage authors to present their results initially with a minimum of discussion so as to invite a range of comments and perspectives from readers.”¹² This is excellent advice but may fall short of an adequate remedy for the fallacy of selective emphasis (because most clinicians read the literature selectively). If journal editors and regulators could turn to a cadre of relatively neutral, uninvested clinicians with special methodologic expertise, then perhaps the threat of preoccupation bias would be mitigated even further.

To effect such a scenario, two strategies suggest themselves. First, medical centers and universities could distinguish between two types of clinical role or faculty appointment: clinician-researcher and clinician-interpreter. Second, medical journals, medical societies, and/or government regulators could assemble boards of expert clinician-interpreters to review scientific studies and make recommendations for practice or public policy. Britain’s National Institute for Clinical Excellence—which provides national guidance on individual technologies, the management of specific conditions, and clinical audit—might exemplify this sort of project, if it were to recruit effective clinician-interpreters to develop guidelines and review the literature.

Clinician-researchers would continue with their current responsibilities and would be free (or even encouraged) to collaborate with private, for-profit industry. Probably most clinician-researchers would continue to be superspecialists. Clinician-interpreters, on the other hand, would be committed to attitudes of economic impartiality, balanced skepticism, and methodologic rigor. The best clinician-interpreters would be experienced generalists skilled in evaluating study design and addressing questions of external validity. (The external validity of a study is the degree to which results of the study apply in actual practice settings.) Faculty in internal medicine, family practice, general pediatrics, and emergency medicine could be ideally suited. To guarantee familiarity with a wide range of practice settings, the recruitment of clinician-interpreters from rural regions or other settings outside the academy might also be desirable.

When government agencies such as the Food and Drug Administration (FDA) seek expert advice, they could turn to such panels of clinician-interpreters. This policy would be a significant departure from current practice. When the Peripheral and Central Nervous System Drugs Advisory Committee (of the FDA) considered the



Does this education campaign show protreatment bias?

use of tissue plasminogen activator (tPA) for acute stroke, it heard mostly from clinical investigators involved in the NINDS trial (the only major trial in which tPA showed significant benefit over nontreatment). Most of these investigators were also employed by Genentech (which markets tPA). The composition of the advisory committee was itself skewed, consisting entirely of neurologic specialists without a single emergency physician or other generalist (transcript of Advisory Committee meeting, June 6, 1996, open committee discussion on Product License Application 96-0350 for Activase [alteplase], Genentech, for management of acute stroke. Obtained from FDA, Bethesda, MD).

Interestingly, the FDA's advisory committee invited public participation, but only Karen Putney of the National Stroke Association spoke up. Her comments nicely illustrate the threat of publicity bias and pretreatment bias:

[National Stroke Association] understands that finding a treatment for acute ischemic stroke for which there is yet no approved therapy will do more than anything else to improve public awareness and understanding, compel the medical community to treat stroke emergently, and improve patient outcome. This study heralds a new approach to stroke and carries the hope of transforming the hopelessness surrounding stroke into active, aggressive, and effective intervention to salvage brain tissue, reduce disability, and save lives.

We see here the usual false dogmas about thrombolysis for stroke: first, that improving public awareness about stroke is so important that it should be a factor in determining whether the use of a dangerous drug such as tPA is approved; second, that tPA saves lives; and finally, that the medical community is remiss if it does not incorporate the new technology quickly into its standard of care. These are the sort of errors that clinician-interpreters would be trained to avoid.

The FDA is not the only organization that would benefit from a panel of clinician-interpreters. When the American Heart Association examined the use of thrombolytic therapy for acute stroke in October 1999, they recruited an emergency physician—Jerome R Hoffman—but then dropped his name from their list of panel members when he refused to sign the resulting recommendations (with which he disagreed).²¹ Initially, Hoffman was asked to submit a rebuttal essay, but his submission was never published. Later, he asked if the American Heart Association would publish a shorter one- to two-paragraph dissent alongside the recommendations. When this offer was refused, he requested that the following statement be appended to the document: “Jerome R Hoffman also participated in the panel but disagrees with the recommendations contained in this paper.” This request was also denied.

CONCLUSION

The fallacy of selective emphasis is an important source of interpretation bias that might be ameliorated by distinguishing between professional clinician-interpreters and clinician-researchers and by recruiting interpreters who are generalists with expertise in methodology. This strategy would integrate nicely with efforts to reduce other sources of interpretation bias, because nonresearchers are less apt to have financial conflicts of interest and may be less prone to expectation bias.

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