Key concepts for informed health choices. 1.2: Seemingly logical assumptions about research can be misleading

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This is the second of four essays in this series explaining key concepts that can help you avoid being misled by untrustworthy treatment claims. In this essay, we explain how five seemingly logical assumptions about research can be misleading. These assumptions are that:

- a plausible explanation is sufficient,
- association is the same as causation,
- more data is better data,
- a single study is sufficient, or
- fair comparisons are not applicable in practice.

The basis for these concepts is described elsewhere.¹

Do not assume that a plausible explanation is sufficient

Treatments that should work in theory often do not work in practice or may turn out to be harmful. A plausible explanation of how or why a treatment might work does not prove that it actually does work, or that it is safe. For example, cutting someone to make them bleed (bloodletting) used to be a common treatment for lots of problems. People believed it would rid the body of ‘bad humours’, which is what they thought made people sick. But bloodletting did not help. It even killed people, including George Washington, the first president of the United States.² His doctors drained 40% of his blood to treat a sore throat!

A more recent theory was that operating on blocked tubes (arteries) that carry blood to the brain would stop damage to the brain (strokes). That makes sense, but when that theory was tested in a fair comparison, researchers found not only that it did not help, but that some people died from the surgery.³

Even if there is plausible evidence that a treatment works in ways likely to be beneficial, the size of any such treatment effect, and its safety, cannot be predicted. For example, most drugs in a class of heart medicines called beta-blockers have beneficial effects in reducing recurrence of heart attacks; but two drugs in the class – pronethalol and practolol – were taken off the market because of unanticipated side effects.⁴ Similarly, it cannot be assumed that a treatment works or does not work based on the type of treatment. For example, it cannot be assumed that all complementary medicines or that all modern medicines do or do not work, or that all vaccines do or do not work. On the other hand, not understanding how a treatment works does not mean that it does not work.

Do not assume that association is the same as causation

The fact that a possible treatment outcome (i.e. a potential benefit or harm) is associated with a treatment does not mean that the treatment caused the outcome. The association or correlation could instead be due to chance or some other underlying factor. For example, people who seek and receive a treatment may be healthier and have better living conditions than those who do not seek and receive the treatment. Therefore, people receiving the treatment might appear to benefit from the treatment, but the difference in outcomes could be because they are healthier and have better living conditions, rather than because of the treatment.

An obvious example of confusing an association with causation would be to assume that going to the
The results of one study considered in isolation can be misleading. A single comparison of treatments rarely provides conclusive evidence; and results are often available from other comparisons of the same treatments. Systematic reviews of all the similar comparisons (‘replications’) may yield different results from those based on the initial studies, and these should help to provide more reliable and statistically precise estimates of treatment differences. Even so, obtaining reliable estimates from treatment comparisons must always consider that important studies may remain unpublished, incompletely published or inaccessible for other reasons.

Randomised trials of oral rehydration solutions (ORS) for children with diarrhoea provide an example of single comparisons of treatments that did not provide conclusive evidence. Children with diarrhoea can become dehydrated. If they become seriously dehydrated, they can die. For more than
Do not assume that fair comparisons are not applicable in practice

Assumptions that fair comparisons of treatments in research are not applicable in practice can be misleading. People may claim that evidence from fair comparisons of treatments cannot be applied to everyday practice. This is likely to be true if there are important differences between the fair comparisons and everyday practice. The effects of treatments are unlikely to differ substantially unless there are compelling reasons for why everyday practice is so different from the fair comparisons that the treatments are unlikely to work in the same way.

Deciding whether there are compelling reasons depends on evidence outside fair comparisons of treatments (for example, basic science research that demonstrates how a treatment causes an outcome) and judgement. Reasons for uncertainty about the applicability of research only become compelling when there is compelling evidence or compelling logical reasons for expecting the effects of a treatment to be substantially different in practice.

For example, human biology tends to be more similar than different across people from different countries, races and ethnicities. So, you would expect medicines to have similar effects most of the time. Thus, it is not necessary to conduct randomised trials of medicines in every country with large samples of people from every race and ethnicity. But there are sometimes important differences. For example, the benefits of lowering elevated blood pressure in reducing strokes and other cardiovascular morbidity and mortality are well established. However, several different types of medicine are used to lower blood pressure and there has been uncertainty about which of these should be used. There has also been uncertainty about whether these medicines worked in the same way in Black people and in non-Black people, particularly for angiotensin-converting enzyme (ACE) inhibitors. This is because ACE inhibitors were found to be less effective for lowering blood pressure in Black people than in non-Black people. For this reason, a randomised trial designed to compare different medicines for lowering blood pressure planned to do a subgroup analysis for Black participants in the trial, which included 33,357 participants (35% Black) in the USA and Canada. The results of this study were largely similar for Blacks and non-Blacks, except for the effect of the ACE inhibitor on strokes. Black participants assigned to the ACE inhibitor were more likely to have a stroke than Black participants assigned to the thiazide diuretic, but this difference was not found in non-Black participants.

Various terms are used to describe the ‘applicability’ of research, including transferability, generalisability, external validity and relevance. Although these terms have been defined differently, checklists designed to assess these concepts include broadly similar criteria. These include differences between fair comparisons and everyday practice in the characteristics of the people, characteristics of the treatments and characteristics of the context. It is possible to generate long lists of things that could potentially be different. For example, differences in patient characteristics could include differences in age, sex, education, income, race, ethnicity, weight, co-morbidity, genetic markers, astrological sign, baseline risk, etc. To avoid being misled by spurious assumptions about fair comparisons not being relevant, only those factors for which there are compelling reasons for why a treatment is unlikely to work the same way in practice as it did in fair comparisons should be considered when assessing the applicability of research results.

It should be noted that most often the relative treatment effect will be similar for people with different baseline risks. Differences in baseline risk will, however, often lead to differences in the absolute effect of treatment.

Implications

- Do not assume that claims about the effects of treatments based on an explanation of how they
might work are correct if the treatments have not been assessed in systematic reviews of fair comparisons of treatments.

- Do not assume that an outcome associated with a treatment was caused by the treatment unless other reasons for the association have been ruled out in a systematic review of fair comparisons.
- Do not assume that an association between a treatment and an outcome found using ‘big data’ or ‘real-world data’ means that the treatment caused the outcome unless other possible reasons for the association have been ruled out.
- The results of single comparisons of treatments can be misleading. Consider all the relevant fair comparisons when making judgements about treatment effects.
- Do not assume that fair comparisons are not applicable because of differences between fair comparisons and everyday practice, unless there are compelling reasons for why treatments would work differently.

**Declarations**

**Competing Interests:** None declared.

**Funding:** This work was supported by the Research Council of Norway (Project numbers 220603/H10 and 284683). The funder had no role in the decision to publish, or preparation of the manuscript.

**Ethics approval:** Not applicable.

**Guarantor:** ADO.

**Contributorship:** ADO, IC, and AD conceptualized, reviewed, and edited drafts of this essay. ADO prepared the first draft.

**Provenance:** Not commissioned; invited article from the James Lind Library.

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