

Mechanisms and EBM:

how a historically tense relationship plays into
(Howick, 2013)

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Outline

- Outline the difficulties with mechanistic reasoning as laid out by the authors
- Suggest why taking this argument as being part of a larger discussion about EBM is warranted by giving an account of the history of EBM's response to mechanistic reasoning
- Show that at least two of four “overlooked problems” of mechanistic reasoning take the stance that mechanistic reasoning is to be thought of in opposition to RCTS and two of four furthermore are present in other methods traditionally and contemporarily venerated by supporters of EBM, like RCTs
- Finally I will discuss the why it matters for policy that we get the reasons to be cautious about mechanistic reasoning right

Article in Question

- Howick J., Glasziou P., and Aronson J.K. “Problems with using mechanisms to solve the problem of extrapolation” *Theoretical Medicine and Bioethics* 2013;34:275–291
- Definition of mechanism: “an inference about an intervention’s clinical effect from alleged knowledge of relevant mechanisms and how they related to one another.” In addition, “The essential feature of mechanistic reasoning is that it involves an inferential chain (or web) linking the intervention with a clinically relevant outcome via (productive!) mechanisms.”

Difficulties with Mechanistic Reasoning

- Our understanding of mechanisms is often (and arguably, likely to remain) incomplete.
- Knowledge of mechanisms is not always applicable outside the tightly controlled laboratory conditions in which it is gained.
- Mechanisms can behave paradoxically.
- Using mechanistic knowledge faces the problem of the ‘extrapolator’s circle’.

History of Mechanistic Reasoning and EBM

- Strong anti-mechanistic reasoning talk in “debut” 1992 article
 - “Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.” (Guyatt, 1992)
 - Bloodletting
 - Antiarrhythmic drugs and CAST (Cardiac Arrhythmia Suppression Trial)
 - emphasis on mechanistic reasoning as opposed to RCTS
- More recent softening
 - Various auxiliary roles for mechanistic reasoning (see list at the end of this article, “sounding the alarm bell”)
 - Still not a part of GRADE
 - Still often treated in opposition to RCTs (rather than a possible part of them)

Analysis of the authors “often overlooked” problems with mechanistic reasoning

- Our understanding of mechanisms is often (and arguably, likely to remain) incomplete. (...Unlike RCTs?)
- Knowledge of mechanisms is not always applicable outside the tightly controlled laboratory conditions in which it is gained (...unlike RCTs?)
- Mechanisms can behave paradoxically.
- Using mechanistic knowledge faces the problem of the ‘extrapolator’s circle’.

Mechanisms can behave paradoxically?

“Besides the epistemological problems with discovering any assumed regularity (such as extreme sensitivity to initial conditions and complex interactions), mechanisms themselves might not behave regularly at all. Mechanisms’ irregular behavior is perhaps best exemplified by paradoxical reactions. Smith et al. have listed many drugs that sometimes worsen the condition for which they are indicated. To name a few, antiepileptic drugs can both prevent and cause seizures, antidepressants can both ameliorate and worsen depressive symptoms, and antiarrhythmic drugs can cause arrhythmias. Even the same molecule can initiate different mechanisms depending on its environment within the body.”

Mechanisms can behave paradoxically?

“A supporter of mechanistic reasoning might, of course, claim that the paradoxical behavior of the mechanism is simply a sign that some other mechanism (or feature of the mechanism) that can explain the paradox is yet to be identified. But this objection seems to rely on a determinist metaphysics that requires independent arguments.”

Conclusions and policy implications

Worry about the extrapolator's circle leads to the proper sort of caution about mechanisms, while traditional insistence on characterizing mechanistic reasoning as the antithesis of RTCs (even when mechanistic reasoning and RCT's may have difficulties in common and mechanistic reasoning may be utilized in the creation and design of RCTs) is an unnecessary restriction.