Evaluating Evidence of Mechanisms in Medicine: A Handbook for Practitioners

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Background:
Earlier work by the group suggested that evidence of mechanisms is helpful in determining whether medical or public health-policy interventions are effective, or whether a particular exposure is carcinogenic [Russo and Williamson, 2007, Clarke et al., 2014].
[Russo and Williamson, 2007, 161]:

“The crucial and equal importance of probabilistic and mechanistic considerations is recognized by the International Agency for Research on Cancer.”
“Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans.” [IARC, 2015]
Similarly, the National Institute for Health and Care Excellence also seems to recognize the importance of evidence of mechanisms [Clarke et al., 2014, 347]:

“In order to formulate recommendations, the guideline committee needs to consider a range of evidence about what works generally, why it works, and what might work (and how) in specific circumstances.” [NICE, 2014]
The current research project: **Evaluating evidence in medicine**.

**Research question:**
How exactly can evidence of mechanisms be considered alongside evidence of correlation to evaluate causal claims in medical research and health policy?
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How to consider evidence of mechanisms

**Efficacy**

Does the effect size and quality of clinical studies establish that the observed correlation is causal?

**No:** Identify evidence for the claim that there exists an appropriate mechanism that can explain the observed correlation.

**Establishing efficacy:**

Efficacy is established if one can establish, in the study population, the existence of a correlation and the existence of a mechanism that can explain this correlation.
How to consider evidence of mechanisms

**External validity**

*Do clinical studies directly establish a suitable association and mechanism in the target population?*

**No:** Identify evidence for the claim that the mechanism of action is sufficiently similar in the target and study populations, and other evidence that there is a correlation in the target.

**Establishing external validity:**

External validity is established if one can establish similarity of relevant mechanisms in the study and target populations, and thereby establish, in the target population, the existence of a correlation and the existence of a mechanism that can explain this correlation.
Identifying evidence of mechanisms in the literature:

A five-step strategy for identifying evidence of mechanisms:

1. **Identify** a number of specific mechanism hypotheses.
2. On the basis of a particular mechanism hypothesis, **formulate** a number of review questions.
3. Use these review questions to **search** the literature.
4. Identifying the evidence most relevant to the mechanism hypothesis by **refining** the results of this search.
5. **Present** the evidence relevant to the mechanism hypothesis.
In evaluating the quality of an item of mechanistic evidence, one should consider the following questions:

1. *How well-established and understood are the methods by which the evidence was produced?*
2. *Can the item of evidence be produced by many independent methods?*
3. *Are the model systems that are used in experimental research representative of humans?*
4. *Can the mechanism be observed operating in many different background contexts?*
### Evaluating evidence of mechanisms

<table>
<thead>
<tr>
<th>Quality level</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>High</td>
<td>Further research is highly unlikely to have a significant impact on our confidence in the claim.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is moderately unlikely to have a significant impact on our confidence in the claim.</td>
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<tr>
<td>Low</td>
<td>Further research is moderately likely to have a significant impact on our confidence in the claim.</td>
</tr>
<tr>
<td>Very low</td>
<td>Further research is highly likely to have a significant impact on our confidence in the claim.</td>
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</table>
Evaluating evidence of mechanisms

The status of a mechanistic claim for efficacy:
A mechanism to account for efficacy is considered established when there are high quality mechanistic studies that confirm all the crucial component features of the mechanism.

The status of a mechanistic claim for external validity:
A mechanism to account for external validity is considered established when high quality evidence establishes the similarity of all the crucial components of the mechanism in the study and target populations.
In order to establish efficacy, one needs to establish that the putative cause and effect are correlated and that there is a mechanism that can account for this correlation.

- More generally, one can take the status of a causal claim to be the minimum of the status of the correlation claim and the status of the mechanistic claim.

**Example:** If a correlation is arguable but the existence of any underlying mechanism is provisionally ruled out, then the causal claim itself is provisionally ruled out.
External validity

In order to establish external validity, one needs to establish similarity of mechanisms between study and target populations.

**Example:** If causation is provisionally established in the target population, established in the study population, and there is established similarity of mechanisms, then causation becomes established in the target population.

For more information:

Please see the latest version of the handbook for practitioners on [ebmplus.org](http://ebmplus.org). Any feedback would be appreciated. Thanks.

