Enhancing the Reproducibility and Transparency of Research Findings

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Opinions I will voice are NOT official opinions of NIH

Shai D. Silberberg
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Trial Watch: Phase II and Phase III attrition rates 2011–2012

Beware the creeping cracks of bias

Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases

Why animal research needs to improve

When Mice Mislead

Believe it or not: how much can we rely on published data on potential drug targets?

Raise standards for preclinical cancer research

False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

Helping editors, peer reviewers and authors improve the clarity, completeness and transparency of reporting health research

Bringing rigour to translational medicine

Drug targets slip-sliding away

Unreliable research

Trouble at the lab

Translating animal research into clinical benefit
Believe it or not: how much can we rely on published data on potential drug targets?

Prinz, Schlange and Asadullah

Bayer HealthCare

*Nature Reviews Drug Discovery*

2011; 10:712-713
Causes for low reproducibility

- Complex innovative techniques
- Confounding variables
- Problems with resources

- Transparency in the reporting of experimental design, conduct, and analysis
- Experimental bias (Human nature)
- Chance and publication bias
“Once a man’s understanding has settled on something (....), it draws everything else also to support and agree with it”

The New Organon, 1620
The Method of Multiple Working Hypotheses

“The moment one has offered an original explanation for a phenomenon which seems satisfactory, that moment affection for his intellectual child springs into existence”

Journal of Geology, 1897

Thomas Chrowder Chamberlin
The reliability of a study is determined by the investigator’s choices about critical details of research design and conduct

“Bias is unintentional and unconscious. It is defined broadly as the systematic erroneous association of some characteristic with a group in a way that distorts a comparison with another group.....”

“.....The process of addressing bias involves making everything equal during the design, conduct and interpretation of a study, and reporting those steps in an explicit and transparent way.”

A LONGITUDINAL STUDY OF THE EFFECTS OF EXPERIMENTER BIAS ON THE OPERANT LEARNING OF LABORATORY RATS*


39 students
14 Rats
Insufficient reporting of methodological approaches is evident for pre-clinical studies.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of publications</th>
<th>Masked assessment of outcome (%)</th>
<th>Random allocation to group (%)</th>
<th>Sample size calculation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease(^{30})</td>
<td>428</td>
<td>95 (22)</td>
<td>67 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Multiple sclerosis(^{11})</td>
<td>1,117</td>
<td>178 (16)</td>
<td>106 (9)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Parkinson's disease(^{31})</td>
<td>252</td>
<td>38 (15)</td>
<td>40 (16)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage(^{32})</td>
<td>88</td>
<td>43 (49)</td>
<td>27 (31)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Sena et al., JCBFM. 2014; 34: 737-742
The fewer methodological parameters are reported, the greater the apparent efficacy!

Effect size for studies of **FK506** (Tacrolimus) in experimental stroke.

*Sena et al., Trends Neurosci 2007; 30: 433-439*
Inadequate reporting is widespread

Journals:
- Cell
- Nature
- Science
- Nature Medicine
- Nature Genetics
- Nature Immunology
- Nature Biotechnology

>500 citations

Figure 1. Methodological Quality of Animal Trials (n=76)

Hackam and Redelmeier, JAMA 2006; 14: 1731-1732
Peer review is the evaluation of work by one or more people of similar competence to the producers of the work.”
The Escalation in Scientific Reporting
(Annual PubMed Publications in English)
Publication Bias

Research Question

hypothesis

Experiments to test the hypothesis

Publish!

File
“We identified 16 systematic reviews of interventions tested in animal studies of acute ischaemic stroke involving 525 unique publications.

Only ten publications (2%) reported no significant effects on infarct volume.”

Sena et al., PLOS Biol 2010; Vol 8 Issue 3
Amyotrophic lateral sclerosis (ALS)

- Death within 5 years of diagnosis
- Central pathological finding is motor neuron death
- 3% of cases from gain of function mutations in SOD1
- Rodents over-expressing SOD1 recapitulate ALS

2002: Minocycline reported to extend survival of SOD1 mice

2003: Randomized placebo controlled trial (412 patients treated for 9 months)

2007: Results of the trial are published - minocycline found to have a harmful effect on patients with ALS
Screened more than 70 drugs in 18,000 mice across 221 studies

Used rigorous and appropriate statistical methodologies

Measured a significant difference in survival between males and females with great sensitivity

No statistically significant positive (or negative) effects for any of the compounds tested, including several previously reported as efficacious.

“...the majority of published effects are most likely measurements of noise in the distribution of survival means as opposed to actual drug effect.“

Scott et al., Amyotroph Lateral Scler 2008; 9: 4-15
The probability of seeing an apparent effect by chance is significant even with 10 animals per group.
The survival benefit of minocycline in the SOD1\textsuperscript{G93A} mouse model of ALS might be due to small sample size and/or Bias

- SOD1\textsuperscript{G93A} transgenic mice
- Started at 5 weeks of age
- i.p. 10mg/kg/day
- 10 animals / group (sex?)
- Not randomized
- Not blinded

- SOD1\textsuperscript{G93A} transgenic mice
- Started at 10 weeks of age
- i.p. 25 and 50 mg/kg/day
- 7 animals / group (females)
- Not randomized
- “The experimenter was blinded to the treatment protocol.”
How to improve reproducibility?

- Lack of transparency in reporting
- Unconscious bias; Deficient experimental procedures
- Chance and Publication bias

Review

Transparency in reporting
“...we will more systematically ensure that key methodological details are reported, and we will give more space to methods sections. We will examine statistics more closely and encourage authors to be transparent, for example by including their raw data.”
Scientific Premise of Proposed Research

The scientific premise for an application is the research that is used to form the basis for the proposed research question.

NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the investigator as crucial to support the application.
Rigorous Experimental Design

NIH expects applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods.

The Flight of Icarus (by Jacob Peter Gowy)
NIH expects that key biological and/or chemical resources will be regularly authenticated to ensure their identity and validity for use in the proposed studies.

Researchers should transparently report on what they have done to authenticate key resources, so that consensus can emerge.

HeLa karyotype

How to improve reproducibility?

Lack of transparency in reporting

Review

Transparency in reporting

Unconscious bias; Deficient experimental procedures

Education

Attentiveness to bias; Good experimental design
How to improve reproducibility?

Lack of transparency in reporting

Unconscious bias; Deficient experimental procedures

Chance and Publication bias

Review

Education

Culture

Transparency in reporting

Attentiveness to bias; Good experimental design

Focus on rigor not glitter
We are all prone to bias!

- Critically assess results/publications
- Rigorously design, execute, and analyze experiments
- Plan experiments to disprove the hypothesis
- Favor robust findings, but.... if it appears to be too good to be true, it probably is!
If you’re doing an experiment, you should report everything that you think might make it invalid – not only what you think is right about it....