The Role of Systematic Reviews

Can Systematic Review of Preclinical Data Assist with Replacement, Refinement, and Reduction of Animal Use in Neuroscience Research?

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July 27, 2011
Rufinamide is a new antiepileptic drug that has been found to be effective in the treatment of partial seizures and drop attacks associated with Lennox-Gastaut syndrome. We performed a quantitative analysis of the efficacy of this new antiepileptic drug from all double-blind, add-on, randomized, placebo-controlled clinical trials published to date. Data from 918 patients were studied. The number of patients per study varied from 25 to 262. Rufinamide was efficacious in doses up to 45 mg/kg daily when provided as adjunctive therapy in patients with Lennox-Gastaut syndrome and other drug-resistant epilepsies. Further studies are needed to confirm and expand these findings.

(Formulaic) Steps of a Systematic Review

1. Exhaustive Search for Published and Unpublished Relevant Data
2. Select Studies for Inclusion that Meet Predetermined Criteria
3. Critically Appraise Studies, Evaluate Quality, and Extract Data
4. Combine Data and Apply Appropriate Statistical Analysis
5. Draw Conclusions and Write Manuscript
6. Update Review as Additional Relevant Studies Emerge
Systematic Review/Meta-Analysis of Clinical Data

• **Routine** approach to evaluating clinical trial data (efficacy of a drug or treatment)

• **Powerful** - as a result of combining multiple studies
  – Have pointed out shortcomings of individual trials
  – Have identified toxicities that appeared to be insignificant in individual trials
  – Have clarified how the design of future trials needs to be modified
  – Have clarified the subpopulations of patients that respond to particular interventions
  – The FDA uses this approach to evaluate drug safety/efficacy across multiple clinical studies and multiple drugs within a class (e.g. black box warnings for rosiglitazone vs. pioglitazone)

• **If preclinical animal studies are used to build a case to the FDA for conducting a clinical trial, why aren’t systematic reviews of the preclinical animal studies required as part of the process?**
Preclinical Research: Narrative reviews are most common

Author (cherry) picks articles and builds a subjective case for his/her view of the results.
Preclinical Research: Narrative reviews are most common

Narrative Reviews

Author follows a pre-determined set of guidelines for including all possible studies, for data analysis, and for making conclusions.

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**Systematic Reviews**

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Formulaic approach minimizes bias, maximizes transparency.
Preclinical Research: Narrative reviews are most common

Narrative Reviews

Author (cherry) picks articles in the literature and builds a (subjective) case for his/her view of the results

Systematic Reviews

Results are objective and quantitative

Formulate approach minimizes bias, maximizes transparency

Author follows a pre-determined set of guidelines for including all possible studies, for data analysis, and for making conclusions.
A Fundamental Problem with the Use of Animals:

Efficacy in Animal Studies ≠ Efficacy in Humans

- **Methodological Bias**
  - Poor quality studies are more likely to report an effect
- **Publication Bias**
  - Negative results are rarely published
- **Animal model poorly recapitulates human disease pathogenesis**

- Underpowered clinical trials
- Treatment regimen differs

🚀 Preclinical Systematic Review is a tool to quantitatively test each of these issues
Methodological Bias: Effect of Study Quality on Measures of Efficacy

FK506 (macrolide immunosuppressant) in experimental stroke

Sena et al., 2007 – Trends in Neuroscience

Poor Quality studies reported neuroprotection, High Quality studies did not
Quality is Generally Lacking in Preclinical Studies

Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals

Carol Kilkenny¹, Nick Parsons², Ed Kadyszewski³, Michael F. W. Festing⁴, Innes C. Cuthill⁵, Derek Fry⁶, Jane Hutton⁷, Douglas G. Altman⁸

1 The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, United Kingdom, 2 Warwick Medical School, University of Warwick, Coventry, United Kingdom, 3 Pfizer Global Research and Development, Groton, Connecticut, United States of America, 4 Animal Procedures Committee, London, United Kingdom, 5 School of Biological Sciences, University of Bristol, Bristol, United Kingdom, 6 Animals Scientific Procedures Inspectorate, Home Office, Shrewsbury, United Kingdom, 7 Department of Statistics, University of Warwick, Coventry, United Kingdom, 8 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

• 40% of 271 randomly chosen articles did not state hypothesis or objective, or number and characteristics of animals (species/strain, sex, age/weight)

• >85% did not report randomisation or blinding (to reduce bias)

• 30% did not report statistical methods
Methodological Bias: As researchers, we generally study healthy young animals . . .

Empirical Evidence of Bias in the Design of Experimental Stroke Studies: A Metaepidemiologic Approach
Nicolas A. Crossley, Emily Sena, Jos Goehler, Janneke Horn, Bart van der Worp, Philip M.W. Bath, Malcolm Macleod and Ulrich Dimagl
*Stroke* 2008;39;929-934; originally published online Jan 31, 2008;

![Table of Study Results]

**Figure 4.** Effect of including animals with comorbid conditions on effectiveness of stroke treatment intervention in experimental (animal model) studies. Abbreviations are as in the legend to Figure 1.
Minimizing Methodological Bias: Parameters of Study Quality

- Monitoring and maintaining physiological parameters
- Dose-response
- Animals randomized to treatment
- Blinded assessment of appropriate outcomes
- Study of subjects with co-morbidities (e.g., age, high fat diet, hypertension)
- Testing in both genders
- Appropriate time windows for treatment and outcome assessment
- Conflict of interest declaration
- Individual study was peer-reviewed
Preclinical Systematic Review Could Avoid Risk and Cost Associated with Negative Clinical Trials

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram, Khalid S Khan
BMJ, doi:10.1136/bmj.39048.407928.BE (published 15 December 2006)

<table>
<thead>
<tr>
<th>Intervention (No of studies)</th>
<th>Random allocation to group</th>
<th>Adequate allocation concealment</th>
<th>Blinded assessment of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids for traumatic head injury (n=17)</td>
<td>2 (12)</td>
<td>3 (18)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Antifibrinolytic agents (n=8)</td>
<td>3 (38)</td>
<td>0</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Thrombolysis for acute ischaemic stroke (n=113)</td>
<td>43 (38)</td>
<td>23 (20)</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Tirilizad for acute ischaemic stroke (n=18)</td>
<td>12 (67)</td>
<td>1 (6)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Antenatal corticosteroids (n=56)</td>
<td>14 (25)</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>*Bisphosphonates (n=16)</td>
<td>5 (31)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*In accordance with definition by Schulz et al.

Tirilizad not only failed in human trials, but increased the risk of death.

Systematic Review prior to clinical trial would have pointed out the poor quality of the animal studies.
Systematic Review can Test the Predictive Value of an Animal Model for Efficacy in Humans


<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 hr</td>
<td>0.91 (0.78–1.06)</td>
</tr>
<tr>
<td>&gt;4 hr</td>
<td>0.98 (0.79–1.22)</td>
</tr>
<tr>
<td>Use of alteplase</td>
<td>0.90 (0.74–1.08)</td>
</tr>
<tr>
<td>No use of alteplase</td>
<td>0.97 (0.82–1.15)</td>
</tr>
<tr>
<td>NIHSS 6–9</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>NIHSS 10–14</td>
<td>0.92 (0.74–1.13)</td>
</tr>
<tr>
<td>NIHSS 15–19</td>
<td>1.14 (0.83–1.52)</td>
</tr>
<tr>
<td>NIHSS ≥20</td>
<td>1.00 (0.71–1.41)</td>
</tr>
</tbody>
</table>

NXY-059 was effective in animal models, but ineffective in humans. Most preclinical studies were performed in healthy young male animals.
How Can Systematic Review Assist with the 3Rs?

• **Reduce** the ineffective use of animals by:
  - Avoiding duplication, preventing further studies of ineffective interventions
  - Providing a more precise estimate of treatment effect (informing future power analysis)

• **Refine** experimental procedures (e.g. humane endpoints) by:
  - Highlighting how differing methodologies affect measures of efficacy
  - Providing a platform for setting a standard for the methodology of a particular model, and unifying the reporting requirements
  - Providing evidence of the effectiveness of refinements

• **Replace** animal use:
  - Systematic reviews of comparative studies could be used to provide evidence of the validity of studies comparing *in vitro*, invertebrate, or *in silico* data with traditional animal models.
Weaknesses of Systematic Review

- Limited knowledge of statistical methods among basic science researchers
- Value of review can be dependent upon quality of included studies
- Difficulty obtaining unpublished and negative data (repository?)
- Can become out of date quickly – must be pro-active to regularly update (repository for updates?)
- Still susceptible to bias in the selection of studies to include
Integrating Systematic Review into Preclinical Translational Research

• Raise awareness of preclinical systematic review
  – Journal of Neurochemistry Special Issue
  – CAMARADES

• Support from Publishers/Journal Editors
  – Requirements for publishing animal studies (blinding, power analysis, co-morbidities)
  – Include means for publishing negative data
  – Provide a platform to enable easy sharing of primary data, particularly when studies are funded by public agencies.

• FDA requirement as part of approval process for initiating a clinical trial?
  – Responsibility of applicant?

• Requirement as part of IACUC or IRB approval process?

• Requirement for funding of animal studies by NIH/Other Agencies?
  – Including requirement to perform a review prior to embarking on a new study
  – Including posting of primary data to facilitate further review
Support from Publishers/Editors
Journal of Neurochemistry Special Issue (Nov, 2010)

The ease difficulty to readily scientific discerning given the narrative literature are power effects or evidence in the an aneurismatic determination of the future of drug development also need research, contribute experiments.

Amanda T. White and Anne N. Murphy
Department of Pharmacology, University of California San Diego, San Diego, California, USA

Abstract
Vascular dementia illness affects cerebral infarct (i.e., hemorrhage/angiopathy) and herna nant arteriopathy. Closely related cognition models to clinical VCI, covering 16 models. The rationale for these we experience systematic modifying.

Abstract
Thiazolidinediones (TZDs) may prevent or attenuate CNS injury arising from an ischemic event. We performed metaanalysis of experimental studies in which a TZD (either rosiglitazone or pioglitazone) was administered in a rodent model of focal or global cerebral ischemia. Infarct volume was the primary endpoint for analysis of drug efficacy, and neurological outcome was also assessed. We identified 31 studies through the use of PubMed and Embase, 22 of which met our pre-specified inclusion criteria and were analyzed with the Cochrane Review Manager software. Treatment with TZDs decreased infarct volume and improved neurological outcome regardless of study quality, dose timing, or ischemia model (transient or permanent). Rosiglitazone and pioglitazone were similarly effective in reducing infarct volume and protecting neurologic function. Importantly, the collective data suggest that pre-treatment with a TZD is not required for neuroprotection, although additional studies are clearly needed to define the breadth of the therapeutic window. The data warrant further studies into the potential acute use of TZDs for ischemic stroke therapy in the general population.

Keywords: ischemic stroke, meta-analysis, pioglitazone, rosiglitazone, systematic review, thiazolidinedione

Methodological quality of preclinical stroke studies is not required for publication in high-impact journals

Jens Minnerup\textsuperscript{1,4}, Heike Wersching\textsuperscript{1,2,4}, Kai Diederich\textsuperscript{1}, Matthias Schilling\textsuperscript{1}, Erich Bernd Ringelstein\textsuperscript{1}, Jürgen Wellmann\textsuperscript{2} and Wolf-Rüdiger Schäbitz\textsuperscript{3}

\textsuperscript{1}Department of Neurology, University of Münster, Münster, Germany; \textsuperscript{2}Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany; \textsuperscript{3}Department of Neurology, EVK Bielefeld, Bielefeld, Germany

"Study quality was not associated with the impact factor before (b =0.2, P = 0.50) and after adjustment for other study characteristics (b =0.3, P = 0.19). There was a significant association of the number of investigated mechanisms and applied techniques with the impact factor (b = 1.4, P < 0.0001).”

Keywords: impact factor; preclinical studies; stroke; study quality; translation
Support from Publishers/Editors

• Enabling publication of negative data

- *Journal of Cerebral Blood Flow & Metabolism* has introduced a new Negative Results article type, intended to provide a forum for data that did not substantiate the alternative hypothesis (i.e. a difference between the experimental groups), and/or did not reproduce published findings. Negative results articles will be published as a one page summary in the print version with the accompanying full paper published online.

- Other Neuroscience journals are stating a position on publication of negative results: *European Journal of Neuroscience, Translational Stroke Research*

- *Journal of Negative Results in Biomedicine* – part of Biomed Central
How to Implement?

• Do we need a centralized preclinical review consortium (not unlike Cochrane Collaboration for clinical systematic reviews)?
  – With resident statisticians to assist/perform reviews
  – How to fund?
Conclusions

• Systematic Review should be applied to preclinical data in order to:
  – Improve the quality and value of animal studies and support the 3Rs
  – Better inform the timing, design, and benefit of clinical trials

• Path to implementation at FDA, Pharma, publisher, and institutional level?
Thanks!

• Sean P. Murphy, Ph.D.
  – Journal of Neurochemistry, Chief Editor

Supported by NIH-NIDDK STTR 1R42DK081298; American Diabetes Association Research Award 1-08-RA-139
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