Improving animal research using a science driven approach:

Systematic reviews of animal studies

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Why evidence-based animal research

- **Decrease**: waste and unnecessary study duplication
- **Increase**: scientific quality (including the 3Rs)
- **Promote**: responsible & justifiable animal use
Introduction

Aim: Improving animal-based research

2006 - 2012

2012 - now
Dutch surveys on 3R search

How is the search for the 3Rs performed and how are the 3Rs implemented?

• Questionnaires locally and nationally:
  • Leenaars et al. ATLA 2009 – local researchers
  • Van Luijk et al. ATLA 2011 – national researchers
  • Van Luijk et al. LAJ 2013 – animal welfare officers
Dutch 3R Questionnaires

Main findings:

• Need for different strategy per “R”

• No budget/time for specific 3R search

• Personal communication vs. literature search

• Relevant 3R information not found / not used

Leenaars et al. 2009, van Luijk et al., 2011 & 2013
Follow-up: 3R workshop

Participants: Researchers
Animal Welfare Officers
Animal Ethics Committee Members

Main outcome: Separate the 3Rs in daily practice
“Replacement” & “Best Practice”

Ways to improve:
• Transparency & collaboration
• Sharing of data (negative results)
• Experimental design (education)

Are Systematic Reviews the way to go?

Van Luijk et al. 2012
Definitions

• **Systematic Review:**
  - The process of systematically locating, appraising and synthesizing evidence from scientific studies in order to obtain a reliable overview.

• **Meta-analysis:**
  - Combination of results of individual studies in an overall statistical analysis.
Systematic reviews of animal studies

Increase of systematic reviews on animal studies
(Medical intervention studies, n=91)

van Luijk et al., 2014
Added value of Systematic Reviews:

- Provide an overview of available evidence
- Identify knowledge gaps
- Critical appraisal of study quality
- Identify factors influencing treatment efficacy
- Inform experimental design of new studies
Overviews of available evidence

Table 2. Design characteristics of included studies

<table>
<thead>
<tr>
<th>Publication</th>
<th>Gender</th>
<th>n (C)</th>
<th>n (Rx)</th>
<th>Dose range (mg/kg)</th>
<th>Doses in first 24 hr</th>
<th>Time to treatment</th>
<th>Anaesthetic</th>
<th>Permanent or focal ischemia</th>
<th>Route of drug delivery</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilic (1999)</td>
<td>Nk</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0 min</td>
<td>Ketamine</td>
<td>Temporary</td>
<td>Intravenous</td>
<td>Comb</td>
</tr>
<tr>
<td>Ling (1999)</td>
<td>Male</td>
<td>9</td>
<td>31</td>
<td>2.5-10</td>
<td>3</td>
<td>-15 min</td>
<td>Chloral hydrate</td>
<td>Temporary</td>
<td>Subcutaneous</td>
<td>Inf. vol.</td>
</tr>
<tr>
<td>Peker (2000)</td>
<td>Nk</td>
<td>2</td>
<td>6</td>
<td>2.5</td>
<td>4</td>
<td>-20 min</td>
<td>Not known</td>
<td>Permanent</td>
<td>i.p.</td>
<td>Comb</td>
</tr>
<tr>
<td>Berlongan (2000)</td>
<td>Male</td>
<td>11</td>
<td>11</td>
<td>23.2</td>
<td>1</td>
<td>0 min</td>
<td>Halothane</td>
<td>Temporary</td>
<td>Oral</td>
<td>Comb</td>
</tr>
<tr>
<td>Pei (2002b)</td>
<td>Male</td>
<td>21</td>
<td>23</td>
<td>5-50</td>
<td>1</td>
<td>-30 min</td>
<td>Pentobarbital</td>
<td>Temporary</td>
<td>Permanent</td>
<td>Inf. vol.</td>
</tr>
<tr>
<td>Lee (2004)</td>
<td>Male</td>
<td>16</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>90 min</td>
<td>Halothane</td>
<td>Temporary</td>
<td>Intravenous</td>
<td>Comb</td>
</tr>
</tbody>
</table>

Number of animals in control group [n (C)]; number of animals in experimental group [n (Rx)]; dose range; number of doses given in first 24 hr; interval from onset of ischaemia to start of treatment; anaesthetic used; and outcome measure used; Nk, not known; i.p., intraperitoneal.

Melatonin in Stroke

Macleod et al. (2005)
Critical appraisal of study quality

Wever et al. 2015

Reporting and Methodological quality
Systematic reviews of animal studies

Increase of systematic reviews on animal studies
(干预研究，n=91)

van Luijk et al., 2014
Systematic reviews of animal studies

Increase of systematic reviews on animal studies
(Intervention studies, n=91)

Risk of Bias assessment, 48 SRs >1 item:
- Selection bias
- Performance bias
- Detection bias
- Attrition bias

van Luijk et al., 2014
Take home message

Systematic reviews can be a powerful new strategy to:

• Exposes scientific strengths and weaknesses
  *(transparency in study validity)*

• Provide evidence-based input for future research
  *(incl. 3R information)*

However, interpret outcome with caution!
- Low (reporting) quality of animal studies
- Systematic review methodology under development!
Guideline development & training

For intervention studies

- Practical MA-guides
- Risk of Bias assessments Tool
- ARRIVE/GSPC
- Step by step search guide
- Animal filters PubMed/Embase

www.SYRCLE.nl