Why Perform Systematic Review and Meta-Analysis

David Howells
Florey Institute of Neuroscience & Mental Health
Human Nature

“We keep moving forward, opening new doors, and doing new things, because we're curious and curiosity keeps leading us down new paths.”

_Walt Disney_

“The important thing is not to stop questioning. Curiosity has its own reason for existing.”

_Albert Einstein_

“Curiosity is the lust of the mind.”

_Thomas Hobbes_

“An understanding of the natural world and what's in it is a source of not only a great curiosity but great fulfilment.”

_David Attenborough_

“The first and simplest emotion which we discover in the human mind, is curiosity.”

_Edmund Burke_

“Curiosity is natural to the soul of man and interesting objects have a powerful influence on our affections.”

_Daniel Boone_

“Children are remarkable for their intelligence and ardour, for their curiosity, their intolerance of shams, the clarity and ruthlessness of their vision.”

_Aldous Huxley_

“Leisure and curiosity might soon make great advances in useful knowledge, were they not diverted by minute emulation and laborious trifles.”

_Samuel Johnson_

**NOVELTY - RISK TAKING - REWARD**
PubMed comprises biomedical literature from MEDLINE, life science journals, and online books.

**Citations per year**

- **734,000 in 2013**

**Total Citations**

- >24 Million Citations in 2014

**Journals Indexed**

- 5,642 Journals in 2014
In Europe, brain diseases account for 35% of all disease burden.


In 2010, brain disease cost Europe €798 billion.


In 2012 alone >70,000 papers used the word “brain” in the title, abstract or key words.

I could potentially read ~2000 papers/year (30 minutes each and half my working time)

Therefore I have to be very selective in what I read!!
"In small mammals, a precipitous decrease in body temperature is common during anesthesia because their high-surface-area-to-mass ratio makes thermo-regulation difficult, a phenomenon compounded by the use of unwarmed gases during inhalational anesthesia (Haskins and Patz, 1980). With agents such as sodium pentobarbital, the core temperature can decrease by 3.5°C to 4.5°C within an hour and brain temperature can be 0.3°C to 0.4°C lower (Kiyatkin and Brown, 2005). As cooling can be profoundly neuroprotective (van der Worp et al, 2007), preclinical evaluation of neuroprotectants should at some stage incorporate an evaluation of the impact of body or brain temperature."

However honest, well read or well intentioned the authors:

• The reader doesn’t know why the writer thought things important
• The reader has no knowledge of what was left out or the reasons for doing so.
Systematic Review Provides:

A structured process to identify all data relevant to a specific research question.

Meta-analysis Provides:

A statistical process that provides a summary estimate of the outcomes from a group of studies, and allows these outcomes from different groups of studies to be compared.

Why:

• Getting closer to the truth.

• A better understanding of biology

• Improving human (and animal) health
Statistical Power

Mean + SD

Power = 0.8, Alpha = 0.05

<table>
<thead>
<tr>
<th>Effect size</th>
<th>SD</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>29</td>
<td>WKY 12</td>
</tr>
<tr>
<td>30%</td>
<td>80</td>
<td>SHR 8</td>
</tr>
<tr>
<td>10%</td>
<td>715</td>
<td>WKY 33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SHR 8</td>
</tr>
</tbody>
</table>

Infarct Volume (mm³)

Sprague Dawley | WKY | SHR
------------|-----|-----
1.5h tMCAo (Young) | 12  | 4   |
2h tMCAo (Young)    | 33  | 8   |
2h tMCAo (Aged)     | 295 | 80  |

In my group, detecting a 30% Effect Size in SD rats would require 33 rats/cohopt
Effect of Melatonin on infarct volume in mainly young male Sprague Dawley rats

[We need n=29 to detect 50% Effect]
Emergency Medicine Animal Research: Does Use of Randomization and Blinding Affect the Results?

Vik Bebarta, MD, Dylan Luyten, MD, Kennon Heard, MD

Classification of studies present at the Society for Academic Emergency Medicine (SAEM) annual meetings from 1997 to 2001.

Bias & NXY-059

Systematic review and meta-analysis
- 11 publications, 29 experiments, 408 animals
- Improved outcome by 44% (35-53%)

62% reduction of effect size

Randomisation

Allocation concealment

Blinded assessment

Co-morbidity
- 7% of studies used animals with hypertension
- 77% of patients in SAINT II had a history of hypertension at study entry

Failed Procedure?  
Fantastic Result?

2hrs tMCAo in Wistar rats
78% neuroprotection
Treatment started at 3hrs,
Not significant at 6hrs,
Rats cooled,
No blinding
No randomisation

NXY-059 for Acute Ischemic Stroke
Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Härdemark, M.D., and Warren W. Wasienski, M.D., for the Stroke—Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

BACKGROUND
NXY-059 is a free-radical—trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke.

METHODS
We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range, 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care).

RESULTS
Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo (P = 0.038 by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events were each similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval, −1.4 to 1.1; P = 0.86). Likewise, no improvement was observed according to the Barthel index (P = 0.14). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation (P = 0.001) and symptomatic intracranial hemorrhage (P = 0.036).

CONCLUSIONS
The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial on ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)


NXY-059 for the Treatment of Acute Ischemic Stroke
Ashfaq Shuaib, M.D., Kennedy R. Lees, M.D., Patrick Lyden, M.D., James Grotta, M.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., Tim Ashwood, Ph.D., Warren W. Wasienski, M.D., and Ugochi Emeribe, Ph.D., for the SAINT II Trial Investigators*

BACKGROUND
The free-radical—trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke—Acute Ischemic NXY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of efficacy in a second, larger trial.

METHODS
We enrolled 3306 patients with acute ischemic stroke in a randomized, double-blind trial to receive a 72-hour infusion of intravenous NXY-059 or placebo within 6 hours after the onset of stroke symptoms. Our primary end point was the distribution of disability scores on the modified Rankin scale at 90 days. We examined scores on neurologic and activities-of-daily-living scales as secondary end points. We also tested the hypothesis that NXY-059 would reduce alteplase-related intracranial hemorrhages.

RESULTS
The efficacy analysis was based on 3195 patients. Prognostic factors were well balanced between the treatment groups. Mortality was equal in the two groups, and adverse-event rates were similar. The distribution of scores on the modified Rankin scale did not differ between the group treated with NXY-059 (1588 patients) and the placebo group (1607 patients; P = 0.33 by the Cochran–Mantel–Haenszel test; odds ratio for limiting disability, 0.94; 95% confidence interval [CI], 0.83 to 1.06). Analysis of categorized scores on the modified Rankin scale confirmed the lack of benefit; the odds ratio for trichotomization into modified Rankin scale scores of 0 to 1 versus 2 to 3 versus 4 to 6 was 0.92 (95% CI, 0.80 to 1.06). There was no evidence of efficacy for any of the secondary end points. Among patients treated with alteplase, there was no difference between the NXY-059 group and the placebo group in the frequency of symptomatic or asymptomatic hemorrhage.

CONCLUSIONS
NXY-059 is ineffective for the treatment of acute ischemic stroke within 6 hours after the onset of symptoms. (ClinicalTrials.gov number, NCT00061022.)

Shuaib et al, NEJM (2007) 357, 562-571
OGD: Flushing culture with nitrogen and providing unusable 2-deoxy-D-Glucose.

Oxidative stress: Induced by 50µM H₂O₂

100µM Antioxidant cocktail (ascorbate, reduced glutathione and dithiothreitol).

NXY-059 does not protect human neurons

β Tub

NXY-059

LDH assay of cell death (normalised to uninjured control)

MTT assay of cell survival (normalised to uninjured control)

Control 50µM H₂O₂ 1µM 5µM 10µM 50µM 100µM 300µM 500µM 1mM

Control 300µM NXY-059 AO Control 100µM SNP 300µM NXY-059 AO Control 50µM H₂O₂ 300µM NXY-059 AO Control 90µM H₂O₂ 300µM NXY-059 AO Control
3M Combination Trial

Selection from 1026 candidates:
- Key target mechanisms;
- Reported efficacy in animal stroke;
- Cost and availability;
- Stability;
- Mode of delivery;
- Safety.

Meta-analysis
Magnesium (Excitotoxicity)
(M=25.9%, 95%CI=23.6-28.1%)

Melatonin (Anti-oxidant)
(M=40.0%, 95%CI=38.0-42.1%).

Minocycline (Anti-inflammatory)
(M=30.6%, 95%CI=28.9-32.3%).

Forelimb flexion (Motor deficit)

Sticky-tape test (Sensory neglect)

Time to remove contralateral tape (secs)

Days post surgery

<table>
<thead>
<tr>
<th>n</th>
<th>Statistical Power</th>
<th>Sample Size Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10% 20% 30% 40% 50%</td>
<td>10% 20% 30% 40% 50%</td>
</tr>
<tr>
<td>24 hours</td>
<td>93   0.36 0.89 1 1 1</td>
<td>284 71 32 18 12</td>
</tr>
<tr>
<td>3 days</td>
<td>83   0.28 0.78 0.98 1 1</td>
<td>348 87 39 22 14</td>
</tr>
<tr>
<td>7 days</td>
<td>73   0.13 0.38 0.69 0.91 0.98</td>
<td>845 212 94 53 34</td>
</tr>
<tr>
<td>14 days</td>
<td>62   0.09 0.22 0.43 0.67 0.85</td>
<td>1370 342 152 86 55</td>
</tr>
<tr>
<td>21 days</td>
<td>51   0.08 0.20 0.39 0.61 0.80</td>
<td>1269 317 141 80 51</td>
</tr>
<tr>
<td>28 days</td>
<td>40   0.09 0.23 0.45 0.68 0.86</td>
<td>848 211 94 53 34</td>
</tr>
<tr>
<td>12 weeks</td>
<td>29   0.06 0.11 0.20 0.32 0.47</td>
<td>1614 404 180 102 65</td>
</tr>
<tr>
<td>24 weeks</td>
<td>15   0.04 0.07 0.11 0.15 0.22</td>
<td>2117 532 236 133 85</td>
</tr>
</tbody>
</table>
Systematic review and meta-analysis of data from 21 controlled studies of environmental enrichment


**Rotating Pole Test**
- **Pooled Effect Size**
  - 80.58% (65.2-95.9) n=104 p<0.001

**Limb Placement Test**
- **Pooled Effect Size**
  - 50.6% (35.5-65.6) n=90 p<0.001

**Horizontal Beam Test**
- **Pooled Effect Size**
  - 62.7% (55.3-70.1) n=75 p<0.001

**Ladder Test**
- **Pooled Effect Size**
  - 8.1% (-11.1-27.2) n=59 p=0.41

**Infarct Volume**
- **Pooled Effect Size**
  - 25.1% (3.7-46.6) n=130 p=0.02

**Neurobehavioural Scores**
- **Learning**
  - **Pooled Effect Size**
    - 8.07% (-11.06 to 27.20) n=59 p=0.408
- **Infarct Volume**
  - **Pooled Effect Size**
    - 25.13% (3.71 to 46.56) n=130 p=0.022
Exercise Reduces Infarct Volume and Facilitates Neurobehavioral Recovery


10,071 publications identified systematically

40 publications met inclusion criteria

"Rodent Physiotherapy"

<table>
<thead>
<tr>
<th>Infarct volume</th>
<th>Neurobehavioral score</th>
<th>Neurobehavioral score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect Size</strong> ( % Improvement )</td>
<td><strong>Effect Size</strong> ( % Improvement )</td>
<td><strong>Effect Size</strong> ( % Improvement )</td>
</tr>
<tr>
<td>Pre-ischemia</td>
<td>Post ischemia</td>
<td>Pre-ischemia</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>
Lewis (LEW/N) and Fischer (F344/N) rats are histocompatible inbred strains characterized, respectively, by susceptibility and resistance to inflammatory disease.
Systematic Review and Meta-Analysis of Therapeutic Hypothermia in Animal Models of Spinal Cord Injury

Peter E. Batchelor, P. E., et al.


Results:
- Systemic hypothermia improved behavioural outcomes by 24.5% (95% CI 10.2 to 38.8).
- Regional hypothermia improved behavioural outcomes by 26.2%, but the variance was wide (95% CI 23.77 to 56.2).
- A number of factors potentially influencing efficacy, including depth and duration of hypothermia, animal species, and neurobehavioural assessment.

Meta-Analysis of Pre-Clinical Studies of Early Decompression in Acute Spinal Cord Injury: A Battle of Time and Pressure

Peter E. Batchelor, Taryn E. Wills, Peta Skeers, Camila R. Battistuzzo, Malcolm R. Macleod, David W. Howells, Emily S. Sena


Results:
- Decompression improved behavioural outcome by 35.1% (95% CI 27.4-42.8; I2=94%, p<0.001).
- Measures to minimise bias were not routinely reported with blinding associated with a smaller but still significant benefit.
- Publication bias likely also contributed to an overestimation of efficacy.
- A number of factors affecting outcome, notably compressive pressure and duration (adjusted r2=0.204, p<0.002).
Immediate Cooling and Emergency Decompression (ICED) for the treatment of traumatic spinal cord injury.

Project Hypothesis
That hypothermia delays compressive injury to the injured spinal cord.

Project Aims
To determine the feasibility and safety of early hypothermia following traumatic cervical SCI.

To determine whether early hypothermia (within 2 hours of spinal cord injury) improves long-term clinical outcome in patients’ acute cervical spinal cord injury decompressed within 18h post-injury.

This trial will be the first randomised study assessing the combination of these two interventions to improve outcome in patients with severe SCI.
### FDA drug approvals per year

![FDA drug approvals graph]

<table>
<thead>
<tr>
<th>Year</th>
<th>New molecular entities</th>
<th>Biologics license applications</th>
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<tbody>
<tr>
<td>1996</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>1997</td>
<td>39</td>
<td>6</td>
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<td>1998</td>
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<td>2000</td>
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<td>2002</td>
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<td>2006</td>
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<td>2007</td>
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<td>2008</td>
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<td>6</td>
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<td>2009</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>3</td>
<td>2</td>
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</table>

### Estimates of the cost of drug development
From: Morgan et al, Health Policy 100 (2011) 4-17.

<table>
<thead>
<tr>
<th>Drug phase</th>
<th>Hansen &amp; Chien</th>
<th>DiMasi</th>
<th>DiMasi et al</th>
<th>DiMasi &amp; Grabowski</th>
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<tbody>
<tr>
<td>1963 to 1975</td>
<td>$161,000</td>
<td>$391,200</td>
<td>$92,000</td>
<td>$146,800</td>
</tr>
<tr>
<td>1970 to 1982</td>
<td>$149,800</td>
<td>$73,900</td>
<td>$414,600</td>
<td>$481,900</td>
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<tr>
<td>1983 to 1990</td>
<td>$192,500</td>
<td>$127,500</td>
<td>$578,000</td>
<td>$964,900</td>
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<tr>
<td>1990 to 2003</td>
<td>$498,800</td>
<td>$578,000</td>
<td>$737,000</td>
<td>$164,700</td>
</tr>
</tbody>
</table>

### Success by class for compounds first tested in man from 1992 through to 2009

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Approved molecules</th>
<th>Current success rate (%)</th>
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</thead>
<tbody>
<tr>
<td>Antineoplastic/immunologic</td>
<td>254</td>
<td>18</td>
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<tr>
<td>Cardiovascular</td>
<td>134</td>
<td>4</td>
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<tr>
<td>CNS</td>
<td>235</td>
<td>9</td>
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<tr>
<td>GI/metabolism</td>
<td>120</td>
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<tr>
<td>Musculoskeletal</td>
<td>88</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory</td>
<td>83</td>
<td>4</td>
</tr>
<tr>
<td>Systemic anti-infective</td>
<td>122</td>
<td>19</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>189</td>
<td>21</td>
</tr>
</tbody>
</table>

### Fate of drugs tested for stroke

- Tested in vitro but not in vivo
- Tested in vivo but not taken forward to clinical trial
- Improved outcome in vivo but benefit in clinical trial
- No preclinical development history
- Tissue plasminogen activator
- Stroke Units
- Aspirin
- Decompression

1. 423
2. 229
3. 229
4. 96
5. 15
6. 1

Success rate and cost of capital:
- 12.0% and 8.0%
- 23.0% and 9.0%
- 21.5% and 11.0%
- 21.5% and 11.5%

Total Million US$: $161,000,000,000
Change in standardised death rate/100,000 (ICD 9+10) of UK population normalised to 1994 data.

But:
- ~15 million people have strokes,
- 5.1 million die each year
- 20% die within the first month, 37% in the first year.
- 24-50% remain dependent on others.
- Costs industrialised world US$/266-1038 billion year

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou  
Lancet 2009; 374: 86-89

Questions relevant to clinicians & patients?
- Low priority questions addressed
- Important outcomes not assessed
- Clinicians and patients not involved in setting research agendas

Appropriate design and methods?
- Over 50% studies designed without reference to systematic reviews of existing evidence
- Over 50% of studies fail to take adequate steps to reduce biases, e.g. unconcealed treatment allocation

Accessible full publication?
- Over 50% of studies never published in full
- Biased under-reporting of studies with disappointing results

Unbiased and usable report?
- Over 30% of trial interventions not sufficiently described
- Over 50% of planned study outcomes not reported
- Most new research not interpreted in the context of systematic assessment of other relevant evidence

85% Research waste = over $85 Billion / year