Efficacy of Antidepressants in Animal Models of Ischemic Stroke: A Systematic Review and Meta-Analysis

McCann SK, Irvine C, Mead GE, Sena ES, Currie GL, Egan KE, Macleod MR, Howells DW
Stroke and antidepressants

- Incidence of depression in stroke patients higher than general population
- Effect of antidepressants on stroke patients investigated in several small clinical trials
- More evidence required (Mead et al Cochrane Database 2013)
- FOCUS (Fluoxetine Or Control Under Supervision; UK)
Antidepressants and stroke recovery

How do antidepressants modulate stroke outcome and what are the important treatment parameters?

↑ Cortical excitability
↑ Neuroplasticity
↑ Neurogenesis

Crews and Nixon 2004
To investigate whether there is evidence to suggest that the use of antidepressants in animal models of stroke has the potential to improve stroke outcome.

**Primary outcome measure:** infarct volume

**Secondary outcome measures:** neurobehavioral scores and neurogenesis outcome measures
Publication inclusion

**2016 Results** from electronic database search of PubMed, Embase, ISI Web of Science, and BIOSIS (16-05-13).

- **1368 Results** screened by title and abstract by two independent investigators.
- **138 Results** that implied focal stroke was induced and an antidepressant was used in one of the experimental groups, or where the publication could not be retrieved.
- **44 Results** that used an antidepressant in a treatment group, had an appropriate control and reported outcome measures for neurobehavioral deficit or infarct volume. Data extracted for analysis.

- **648 Duplicate results excluded**

- **1230 Results initially excluded:**
  - clinical study
  - review
  - global ischemia model
  - no antidepressant therapy
  - related to a different disease

- **94 Results excluded after detailed screening:**
  - no control group
  - no single therapy
  - mechanistic study
  - different model (no MCAo)
  - outcome measures not applicable
  - missing key data (N, SD, SE, M)
  - conference abstract that did not contain appropriate data for extraction
  - published later in full
  - other

McCann et al *Stroke* 2014
## Antidepressant categorization

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug</th>
<th>Infarct Volume</th>
<th>Neurobehavioral Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comparison n=animals</td>
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<tr>
<td><strong>TCA</strong></td>
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<td></td>
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<tr>
<td></td>
<td>Amitriptyline</td>
<td>3</td>
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<tr>
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<td>Doxepin</td>
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<td>Nortriptyline</td>
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<tr>
<td><strong>Lithium</strong></td>
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<td><strong>SSRI</strong></td>
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<td>Citalopram</td>
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<td>Escitalopram</td>
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<td>Fluoxetine</td>
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<td>Fluvoxamine</td>
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<td>Sertraline</td>
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<td><strong>SNRI</strong></td>
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<td><strong>DA &amp; SRI</strong></td>
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<td>Selegiline</td>
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<td>TFA</td>
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<td>Wuling capsule</td>
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<td><strong>TREK-1 antagonist</strong></td>
<td>Spadin</td>
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**TCA:** Tricyclic antidepressant  
**SSRI:** Selective serotonin reuptake inhibitor  
**SNRI:** Serotonin-noradrenaline reuptake inhibitor  
**DA & SR:** Dopamine and serotonin reuptake inhibitor  
**MAO:** Monoamine oxidase  
**TFA:** Total flavones of Abelmoschus manihot L. Medic
Effect of antidepressants on infarct volume

- 29 Publications
- 58 comparisons
- 27.3% (95% CI 20.7 – 33.8)
Effect of antidepressants on infarct volume

McCann et al Stroke 2014
Effect of antidepressants on neurobehavioral score

- 33 Publications
- 98 comparisons
- 53.7% (95% CI 46.4 – 61.1)
Effect of antidepressants on neurobehavioral score

- Adjusted effect size = 36.5% (95% CI 28.7 – 44.3)

McCann et al Stroke 2014
Effect of antidepressants on neurobehavioral score

McCann et al. Stroke 2014
Effect of antidepressants on neurobehavioral score

McCann et al Stroke 2014
Effect of antidepressants on neurobehavioral score

McCann et al Stroke 2014
Effect of SSRIs on infarct volume

McCann et al. Stroke 2014
Effect of SSRIs on neurobehavioral score

McCann et al. Stroke 2014
Effect of SSRIs on neurobehavioral score

- Random allocation to group
- Species
- Control of temperature
- Anesthetic without neuroprotection

McCann et al Stroke 2014
## Effect of SSRIs on neurogenesis

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<tr>
<th>Publication</th>
<th>Proliferation</th>
<th>Survival</th>
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</table>

2.2 SD (95% CI 1.3 – 3.0 SD)
Summary, overall analysis

- Improvement with antidepressant treatment in studies that used the chronic mild stress paradigm as well as those that did not

- Infarct volume reduction lower in studies with a higher quality score

- Improvement in neurobehaviour more robust despite evidence for publication bias
SSRIs have a greater effect on functional than structural outcomes

For functional outcomes:

- Largest effects = multiple doses and oral administration
- Time of administration does not affect outcome (first administration from >2 weeks pre-stroke to >1 month post-stroke)
- Effect sizes larger at later time points
- Effect of SSRIs on behaviour independent of tissue salvage
Conclusions

- Animal data in line with current clinical data supporting benefit of antidepressants after stroke
- Marked effect of study quality on structural outcomes
- Support a role for antidepressants to facilitate recovery of function, independent of an effect on mood
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