Opioid self-administration

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The NC3Rs

- UK-based scientific organisation
- Use the 3Rs as a framework to support science, innovation and animal welfare
- Work with research funders, academia, industry and regulators – broad remit
- Budget ~ £7 million per annum
- Activities divided between:
  1. Research funding
  2. Centre-led science programmes

www.nc3rs.org.uk
Background

- Self-administration studies to assess the reinforcing properties of drugs
- NHP is the gold standard but is the rat predictive?
- Previous NC3Rs/Pfizer study showed high concordance between findings from rat self-administration studies and clinical indicators of abuse liability
- Present study: systematic review and meta-analysis to compare the self-administration of opioid drugs in rats and NHPs

**Inclusion criteria:**
- Original research
- Single opioid drug
- Rat or NHP
- Clinical route of administration
- Free-operant
- First order schedule of reinforcement
- Negative control
- Published in English
- Outcome: number of drug doses self-administered

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**Search strategy**

- **PUBMED** 1947 – Apr 2009
- **EMBASE** 1988 – Apr 2009
- **MEDLINE** 1950 – Apr 2009

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**Records identified:** 1114
**Records screened:** 453
**Full text articles assessed for eligibility:** 261

- **Full-text articles excluded based on abstract:** 192
  - Different outcome: 75
  - No control data: 64
  - Results incomplete/unclear: 11
  - Not opioid SA in rat or NHP: 15
  - Duplicate: 3
  - No data: 11
  - Methods: 16
  - Not original research paper: 8

- **Full-text articles included in the meta-analysis:** 58

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**NHP:** 31
**RAT:** 27
**Comparisons:** 464 (223 comparisons)
Influence of drug class on the self-administration of opioids

**NHP (n=464)**
13.98 [10.77-17.18]

**Rat (n=223)**
10.21 [7.71-12.70]
Influence of sex on self-administration of opioids

Rat: males maintained higher levels of self-administration than females

NHP: inconclusive
Dose response curves for the self-administration of morphine

NHP (n=36)

Rat (n=52)
Quality of included studies – risk of bias

- Sample size calculation: All studies reported sample size calculation.
- Randomisation of treatment allocation: Most studies reported randomisation, but some were not reported.
- Allocation concealment: All studies reported allocation concealment.
- Blinding during result assessment: All studies reported blinding during result assessment.
Influence of randomisation on self-administration of opioids

**NHP**
- Randomised: n=12
- Unknown: n=45
- Not randomised: n=407

**Rat**
- Randomised: n=18
- Unknown: n=148
- Not randomised: n=57
Quality of reporting

- Number of comparisons reporting the information

- Number of operant devices
- Strain
- Restraint
- Time out
- Sex
- Training
- Drug history
- Feeding restriction
- Light/dark phase

Rat - NHP

Number of comparisons reporting the information

- 0
- 100
- 200
- 300
- 400
- 500
- 600
Quality of reporting - ARRIVE guidelines

Use of systematic reviews and meta-analysis in currently hindered by the poor reporting quality of animal studies.

More information needed:
- To assess internal validity of included studies
- To assess sources of heterogeneity

ARRIVE guidelines were developed to improve the reporting of biomedical research using animals

- 20 items checklist - consensus between
  - Scientists
  - Statisticians
  - Journal editors
  - Research funders
Who uses the ARRIVE guidelines?

430 journals | 35 UK universities | funders | learned societies

Over 5,000 copies sent to 25 countries | Webpage visitors from 110 countries
Thank you!

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Further information

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3Rs Prize 2014
International prize for excellence in 3Rs research

CALL FOR NOMINATIONS

£20k Prize awarded for an outstanding primary research paper reporting an original scientific or technological advance with the potential for significant impact on one or more of the 3Rs.

Papers published in a peer-reviewed journal in any discipline between 1 September 2011 and 1 September 2014 are eligible.

Application deadline: 5 December 2014 16:00 GMT
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