Universität Zürich[UZH]

UZH Center for Reproducible Science

Systematic reviews of animal studies as avenue to reproducible and translatable preclinical research

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Reproducibility in biomedical research, April 12, 2024

STRIDE-Lab

Vision: Foster the development of therapies to treat human diseases (Translation).

Methods: Evidence synthesis and data science.

Impact: Benefit welfare of experimental animals and contribute to better treatments for patients.

https://stride-lab.pages.uzh.ch/website/

1959: Russel and Burch's 3Rs

Replace

Reduce

Refine

Russell, W.M.S. and Burch, R.L., (1959) *The Principles of Humane Experimental Technique*

Harm-benefit analysis

Primary research

Rosso et al, 2024; Würbel 2017; Eggel and Würbel 2021

What are systematic reviews?

- A research summary that addresses a focused question in a structured and reproducible manner.
- Purpose: uncovering problems in preclinical research, informing best practice guidelines, reducing research waste, guiding translational research, and enhancing reproducibility.

01	DEFINE A SPECIFIC RESEARCH QUESTION	06	SCREEN FULL TEXTS FOR RELEVANCE
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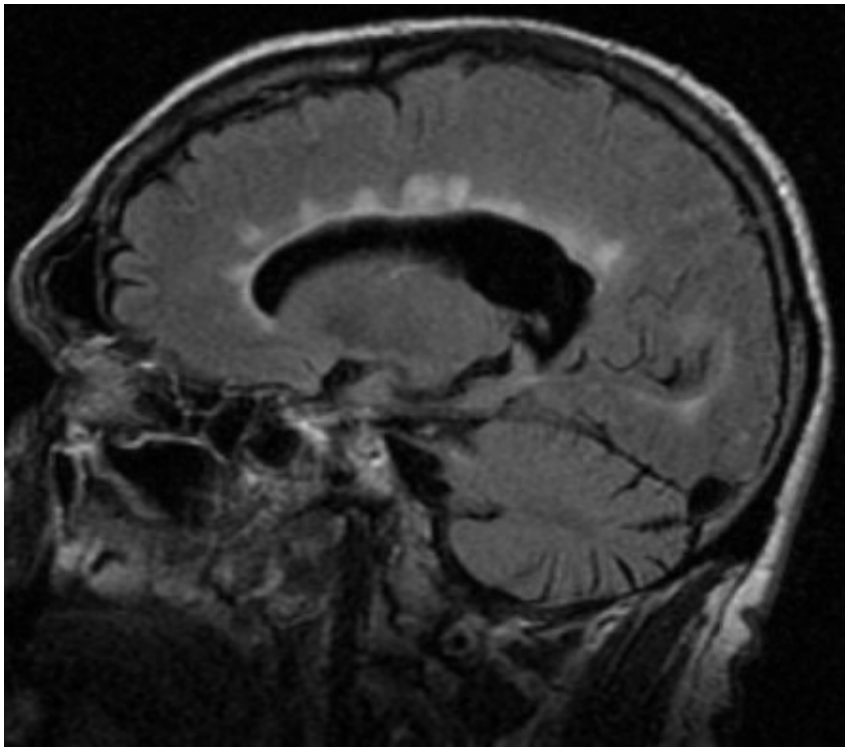
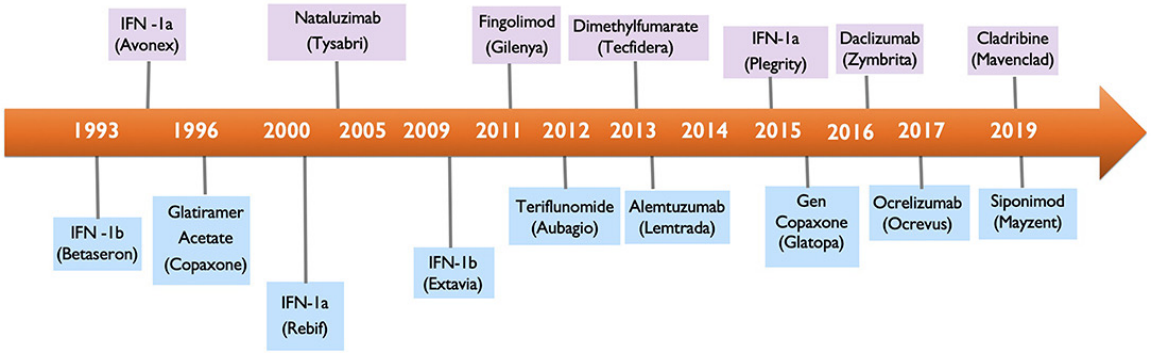
Rosso et al, 2024

Assessing the predictive translational power of animal models in multiple sclerosis drug development: A systematic review and meta-analysis

Ingrid Berg



Approved multiple sclerosis drugs



Failed multiple sclerosis drugs

Goal: systematically compare animal experiments of approved versus failed multiple sclerosis drugs

Melamed & Lee, 2020; Berg et al, *submitted*, 2024

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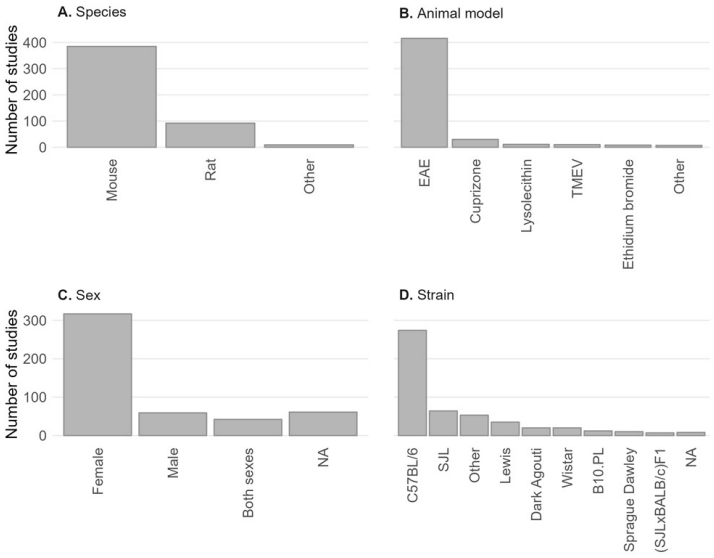

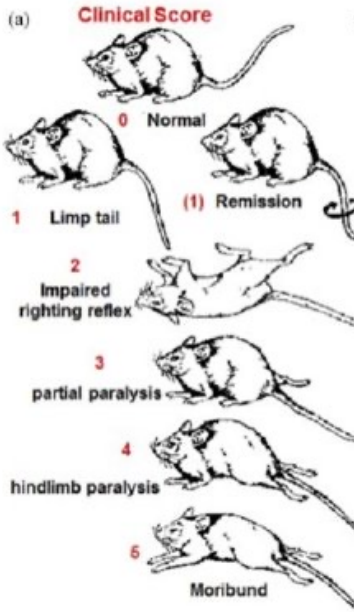

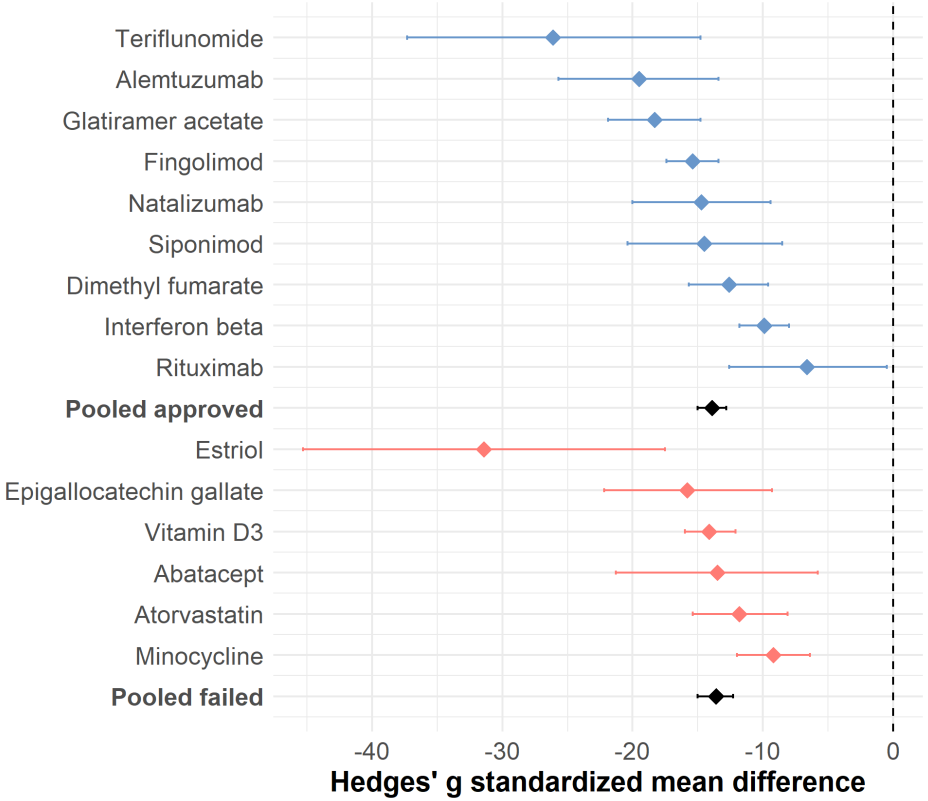

Berg et al, *submitted*, 2024; Burrows et al, 2018

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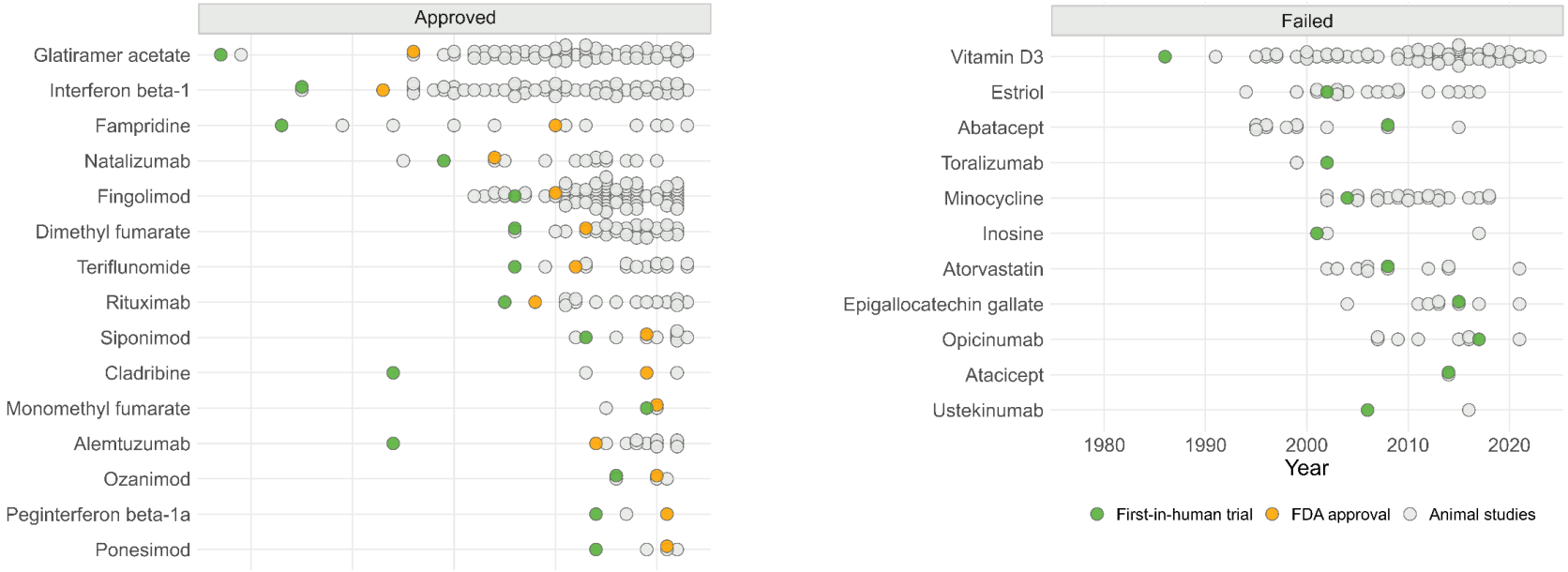


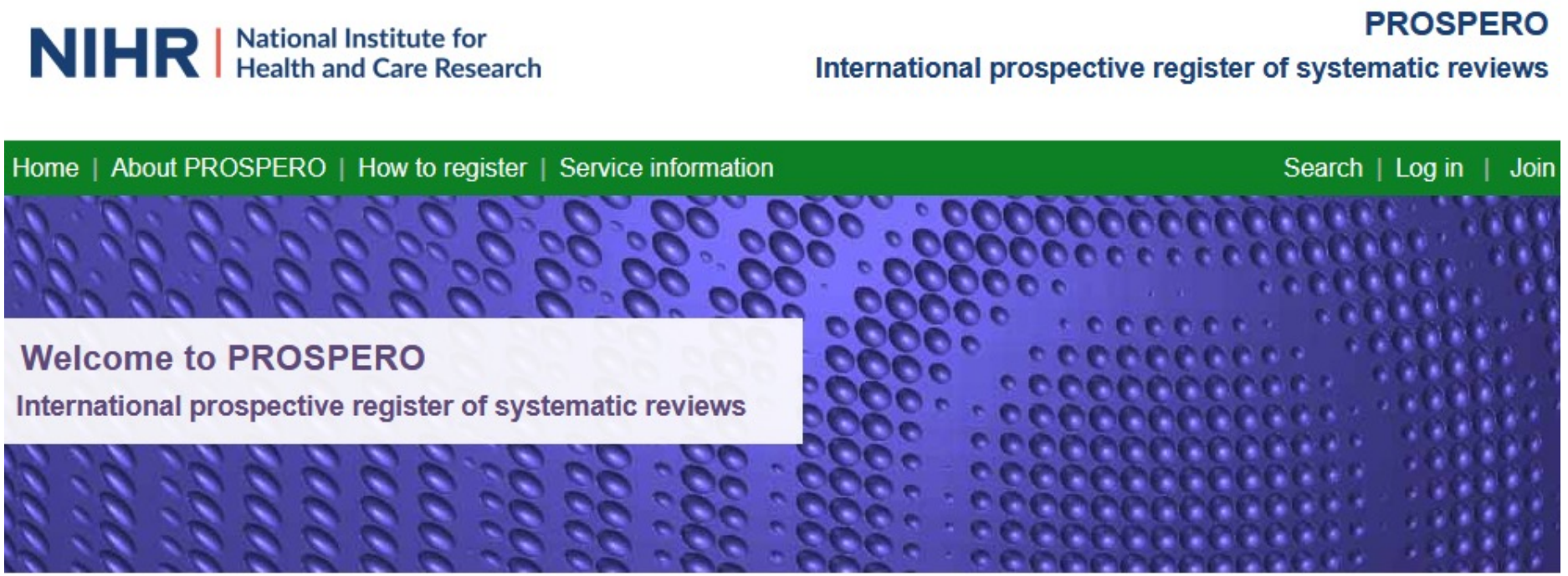
90% of animal experiments have been conducted…

- …AFTER first-in-human trial
- …AFTER regulatory approval

Berg et al, *submitted*, 2024

How long does it take to complete and publish an animal systematic review?

Julia Bugajska



Bugajska et al, *submitted*, 2024

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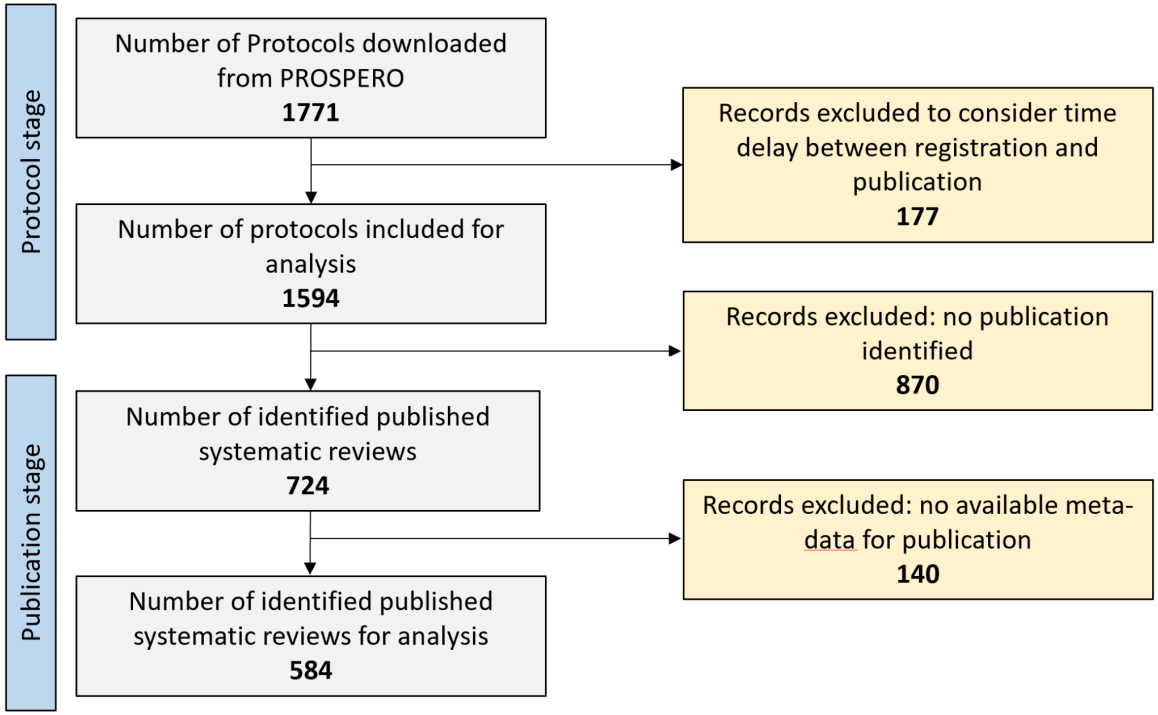

Bugajska et al, *submitted*, 2024

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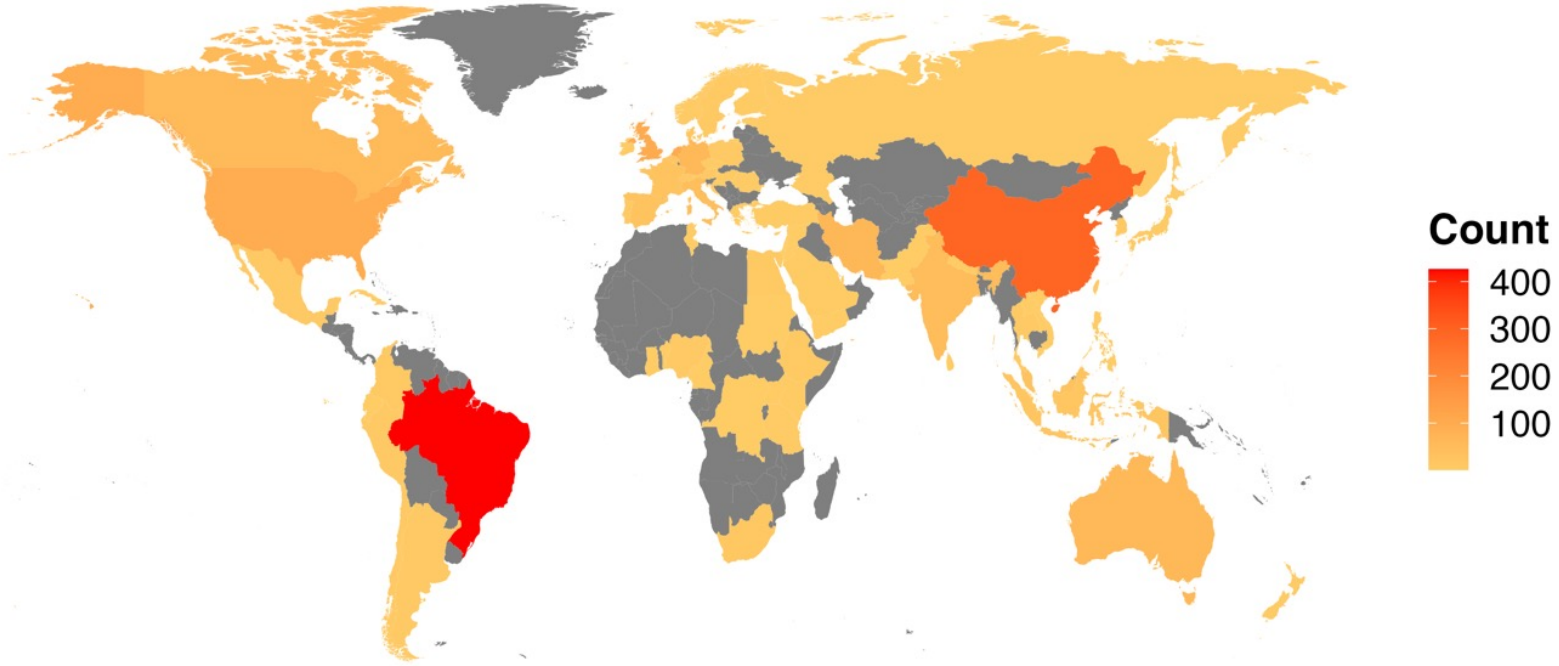

Bugajska et al, *submitted*, 2024

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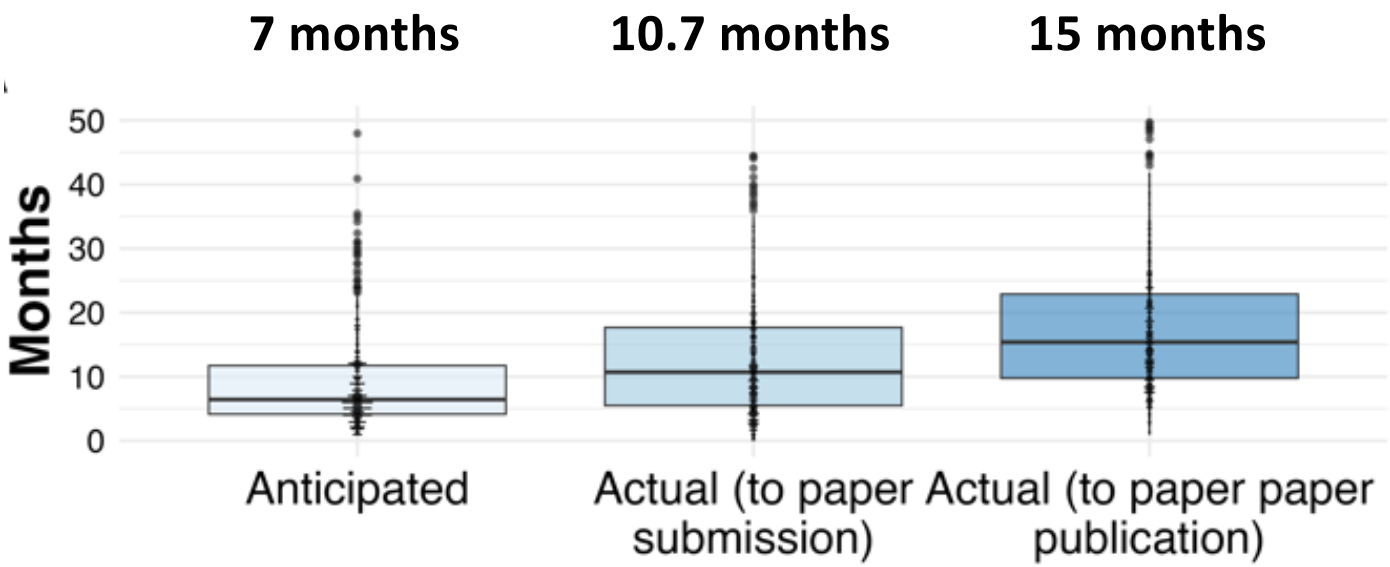
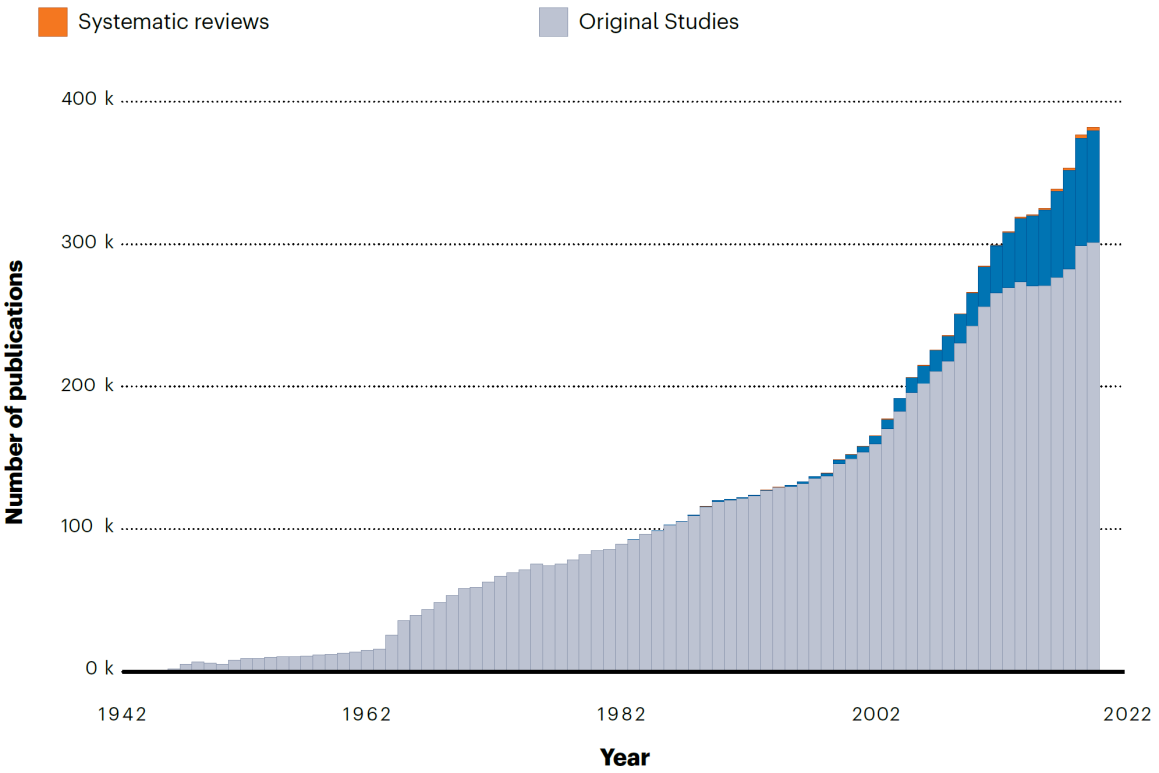


10.7 months (might vary for individual cases!)

Bugajska et al, *submitted*, 2024

Data deluge in biomedicine as barrier for reproducibility



2023

Ineichen et al, 2023

Automation of systematic reviews?

Simona Doneva

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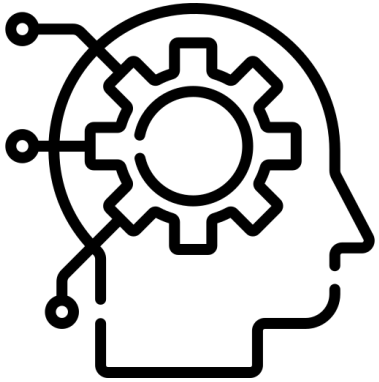
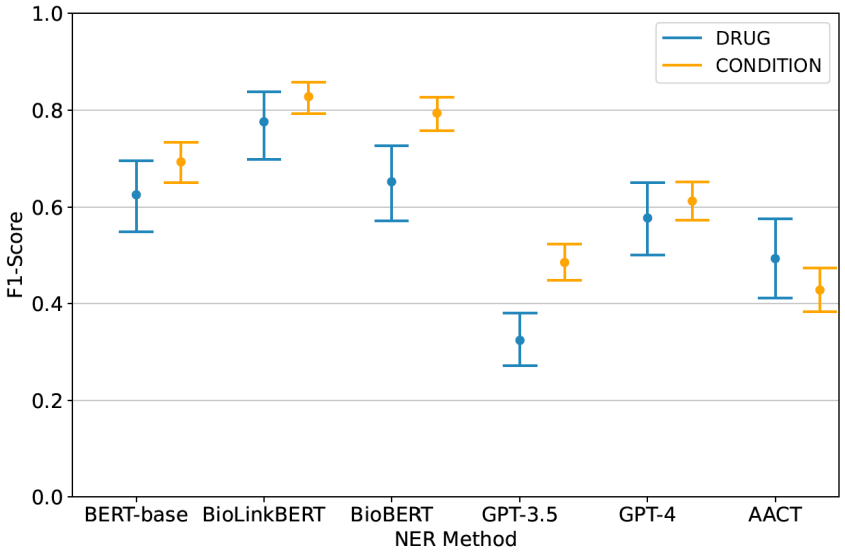


Data extraction of clinical trial registries using large language models

Simona Doneva



Disease

NER Method	Exact	Partial
BERT-base	0.61 (0.53, 0.68)	0.63 (0.55, 0.70)
BioLinkBERT	**0.76** (0.68, 0.83)	**0.78** (0.70, 0.84)
BioBERT	0.63 (0.55, 0.70)	0.65 (0.57, 0.73)
GPT-3.5-turbo	0.26 (0.22, 0.32)	0.33 (0.27, 0.38)
GPT-4	0.45 (0.42, 0.57)	0.58 (0.50, 0.65)
AACT	0.39 (0.32, 0.47)	0.49 (0.41, 0.58)

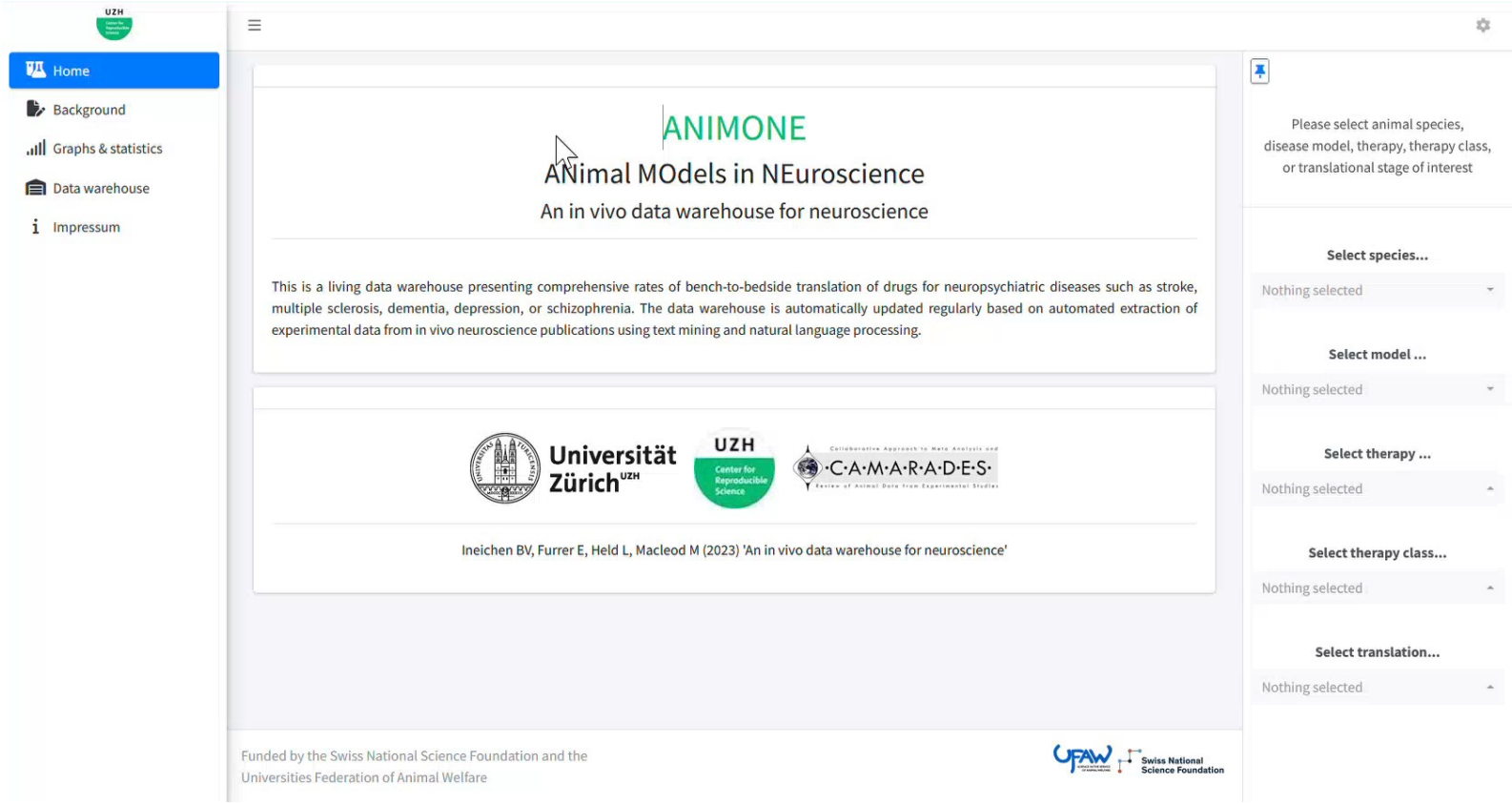
Drug

NER Method	Exact	Partial
BERT-base	0.65 (0.60, 0.69)	0.69 (0.65, 0.73)
BioLinkBERT	**0.78** (0.74, 0.81)	**0.83** (0.79, 0.86)
BioBERT	0.73 (0.69, 0.77)	0.79 (0.76, 0.83)
GPT-3.5-turbo	0.40 (0.36, 0.43)	0.49 (0.45, 0.52)
GPT-4	0.49 (0.45, 0.53)	0.61 (0.57, 0.65)
AACT	0.34 (0.30, 0.39)	0.43 (0.38, 0.47)

Doneva et al, *submitted*, 2023

https://first-layer.shinyapps.io/uzh-animone/

A data warehouse presenting therapy translation for multiple sclerosis



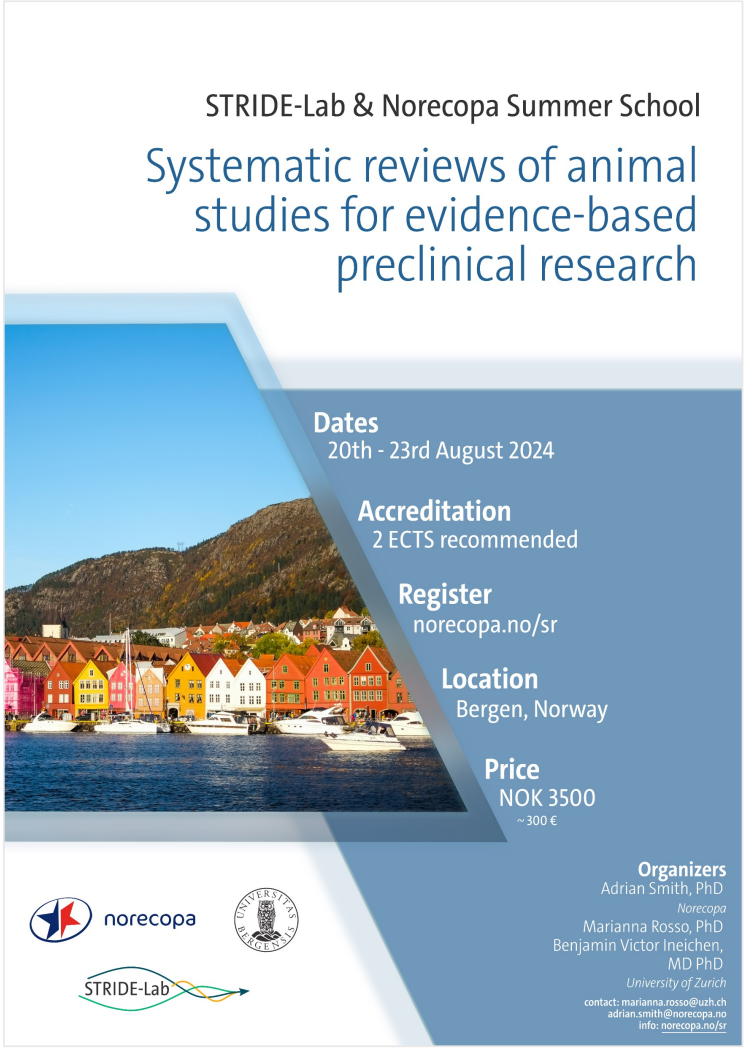
What to remember from this talk

- Systematic reviews…:
  - … Can assess translational hurdles of preclinical research.
  - … Can benefit animal welfare.
  - … Can be conducted within a reasonable time frame.
  - … Can potentially be (semi-)automated.
  - … Can foster reproducible research.

Interested in systematic reviews?

C·A·M·A·R·A·D·E·S
Z·U·R·I·C·H

The **C**ollaborative **A**pproach to **M**eta **A**nalysis
and **R**eview of **A**nimal **D**ata from **E**xperimental **S**tudies
https://camarades.ch



Link to registration:
https://norecopa.no/summer-school-on-systematic-reviews-of-animal-studies/

Thank you

C·A·M·A·R·A·D·E·S
Z·U·R·I·C·H

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ANIMONE consortium

STRIDE-Lab

Funding

UFAW
SCIENCE IN THE SERVICE OF ANIMAL WELFARE

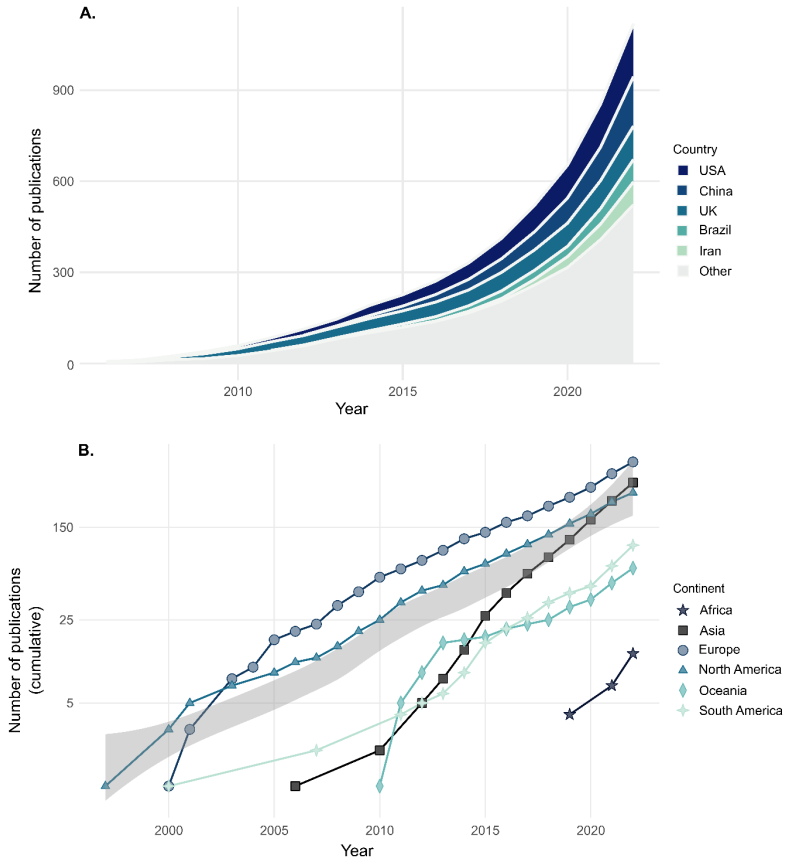
Swiss National Science Foundation

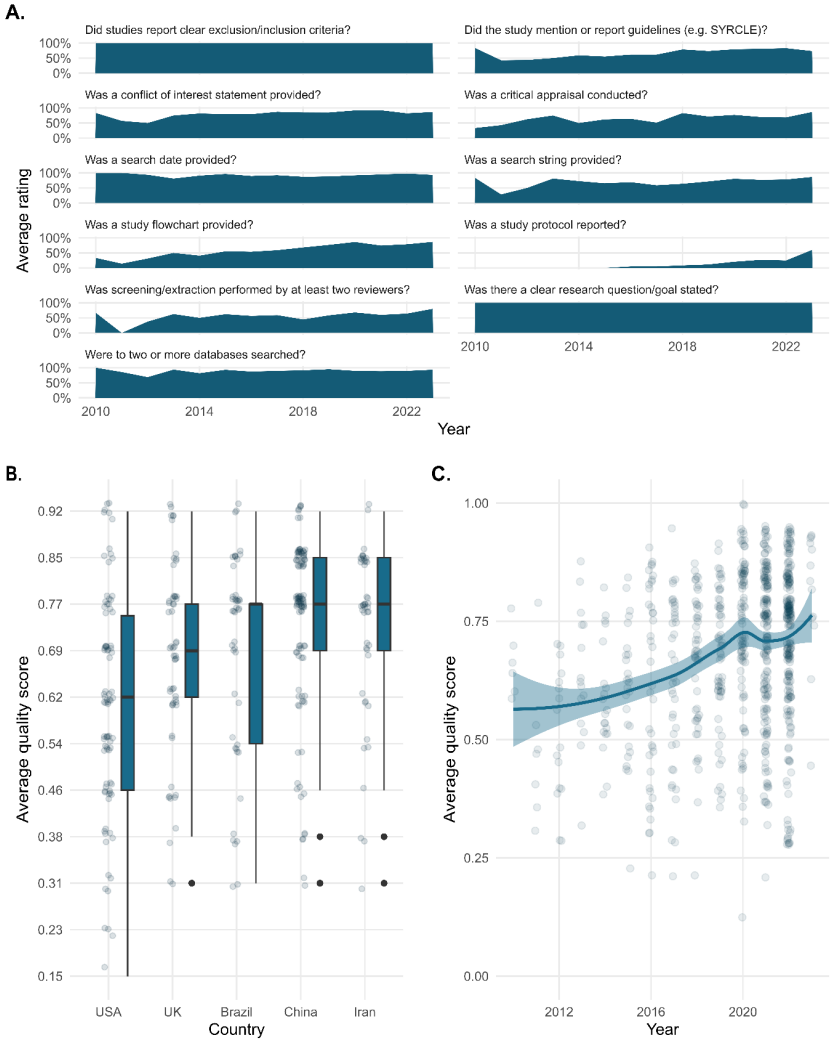
USZ Universitäts Spital Zürich

MS Schweizerische Multiple Sklerose Gesellschaft

Universität Zürich[UZH]

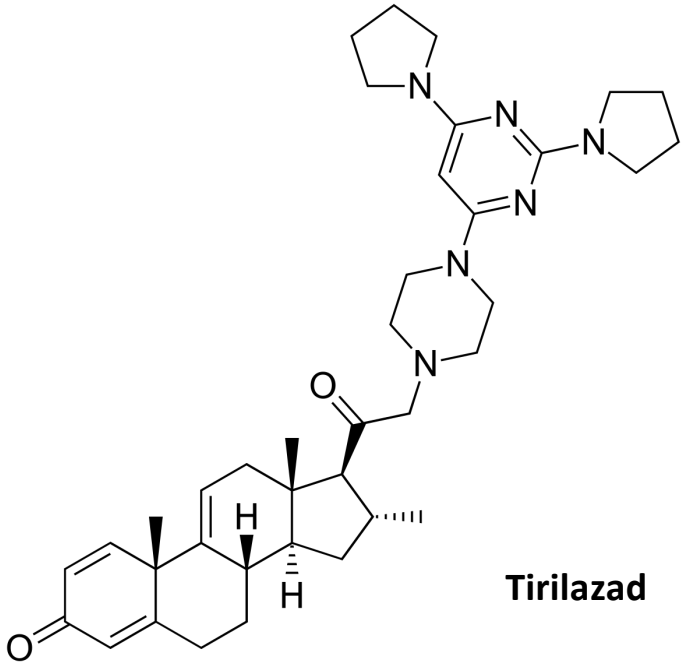
Umbrella review





Hild und Brüschweiler et al, *submitted*, 2024

Systematic reviews uncovering fundamental problems in translational research



Tirilazad

TABLE 1. Study Characteristics

Author	Year	Drug	Species	Sex	N (C)	N (Rx)	Dose Range	Time of Admin, min	Anaesthetic	Type of Ischemia	Route of Delivery	Outcome Measure(s)
Alessandri	2000	Tirilazad	Rat	Male	6	6	29 mg/kg	15	Halothane	Permanent	IV	Infarct Volume
Beck	1991	Tirilazad	Rat	Unknown	12	10	4–40 mg/kg	−30	Halothane	Permanent	IP	Infarct Volume
Gross	1997	Tirilazad	Rabbit	Both	8	8	3 mg/kg	210	Ketamine	Thrombotic	IV	Infarct Volume
Hellström	1994	Tirilazad	Rat	Male	8	10	6 mg/kg	10	Halothane	Permanent	IV	Infarct Volume Neurological Score
Lythgoe	1990	Tirilazad	Rat	Male	7	7	26 mg/kg	10	Pentobarbital	Permanent	IV	Infarct Volume
Öktem	2000	Tirilazad	Rabbit	Unknown	6	6	6 mg/kg	15	Ketamine	Permanent	IV	Infarct Volume Neurological Score
Orozco	1995	Tirilazad	Rabbit	Unknown	10	10	3 mg/kg	120	Acepromazine	Thrombotic		Infarct Volume
Park	1994	Tirilazad	Rat	Male	7	7	1.89–18.9 mg/kg	15	Halothane	Permanent	IV	Infarct Volume Neurological Score
Schmid-Elaesser	1998	Tirilazad	Rat	Male	10	10	6 mg/kg	−15	Halothane	Reversible	IV	Infarct Volume
Schmid-Elaesser	1999b	Tirilazad	Rat	Male	10	10	6 mg/kg	−20	Halothane	Reversible	IV	Infarct Volume Neurological Score
Schmid-Elaesser	1999a	Tirilazad	Rat	Male	10	10	6 mg/kg	−15	Halothane	Reversible	IV	Infarct Volume Neurological Score
Schöller	2004	Tirilazad	Rat	Male	12	17	6 mg/kg	−30	Halothane	Permanent	IV	Infarct Volume Neurological Score
Takeshima	1993	Tirilazad	Cat	Female	7	9	1.5 mg/kg	0–70	Halothane	Reversible	IV	Infarct Volume
Umemura	1994	Tirilazad	Rat	Male	5	5	1 mg/kg	4	Pentobarbital	Thrombotic	IV	Infarct Volume
Wilson	1992	Tirilazad	Rabbit	Both	10	8	6 mg/kg	−30	Ketamine	Thrombotic	IV	Infarct Volume
Xue	1991	Tirilazad	Rat	Male	19	19	20–30 mg/kg	360	Halothane	Reversible	IP	Infarct Volume
Zausinger	2003a	Tirilazad	Rat	Male	10	10	6 mg/kg	−20	Halothane	Reversible	IV	Infarct Volume Neurological Score
Zausinger	2003b	Tirilazad	Rat	Male	12	10	6 mg/kg	0–300	Halothane	Reversible	IV	Infarct Volume Neurological Score

IP indicates intraperitoneal; IV, intravenous.

Time of Admin, min

15
−30
210
10
10
15
120
15
−15
−20
−15
−30
0–70
4
−30
360
−20
0–300

Sena et al, 2007