# SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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| Item # | Section/Subsection/Item | Description | Check for approval |
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| | A. General | | |
| 1. | Title of the review | A systematic review and network meta-analysis of the predictive validity of the animal models of depression | |
| 2. | Authors (names, affiliations, contributions) | Alana Castro Panzenhagen[a]: study design, records selection, solving records selection discrepancies, data analysis, manuscript writing.<br>Roberto Farina de Almeida[b]: study design, records selection, solving discrepancies in risk of bias assessment, manuscript writing.<br>Douglas Leffa[c]: records selection, data extraction, manuscript writing.<br>Fernando Godoy Pereira das Neves[d]: records selection, data extraction, manuscript writing.<br>José Cláudio Fonseca Moreira[a]: study design, study coordination, manuscript revision.<br>Flávio Shansis[d]: study design, records selection, study supervision, manuscript writing and revision.<br><br>[a]Programa de Pós-graduação em Ciências Biológicas: Bioquímica, Universidade Federal do Rio Grande do Sul<br>[b]Departamento de Ciências Biológicas, Universidade Federal de Ouro Preto<br>[c]Programa de Pós-graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul<br>[d]CEntro de PEsquisa Translacional em Transtornos de Humor e Suicídio (CEPETTHS). Programa de Pós-graduação em Ciências Médicas, Universidade do Vale do Taquari | |
| 3. | Other contributors (names, affiliations, contributions) | Hanny Kirszenworcel Pereira[e], Isabel Christina de Carvalho Cyrne[e], Luciano Gouvêa de Moraes Silva[e], Marina Zanotto[e], Matheus Arcari[e], Amanda Cristina Wiest[e], Augusto Cezar Sartori Maffini[e], Eliege Bortolini[e], Luiza Lucas[e], Júlia Souza Rosa Martins[b], Arthur Ripari Tribuzi[b], Dênio de Oliveira Júnior[b], Gabriela Esper Kallás Lopes[b]: study selection, data extraction, and risk of bias assessment.<br><br>[e]Curso de Medicina, Universidade do Vale do Taquari | |
| 4. | Contact person + e-mail address | Alana Castro Panzenhagen (alana.castro@ufrgs.br) | |
| 5. | Funding sources/sponsors | This work is supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Universidade do Vale do Taquari. | |
| 6. | Conflicts of interest | The authors declare no conflicts of interest | |
| 7. | Date and location of protocol registration | - | |
| 8. | Registration number (if applicable) | - | |

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| 9. | Stage of review at time of registration | Systematic searches - complete, screening for inclusion - started, data extraction - not started. | |
| | B. Objectives | | |
| | Background | | |
| 10. | What is already known about this disease/model/intervention? Why is it important to do this review? | Major depressive disorder (MDD) is a highly impairing condition that affects up to 364 million people worldwide [1]. Appropriate treatment for MDD therefore poses a great health and also economic concern. In the US alone, it is estimated that the costs due to MDD impairing effects are as high as $210.5 billion per year [2]. Moreover, approximately 50% of patients do not respond to first and second line pharmacological treatments, leading to overall low response rates [3]. These factors raise major concerns in the field, pointing to the desperate need for antidepressant drug discovery. Animal models have been key to understanding the pathophysiology of psychiatric disorders, but even more crucial to the investigation of new treatment approaches [4,5]. Notwithstanding, models are not always ideal and should follow a set of rules and validities for them to be accepted as reliable tools. Although some authors have stated that there are several validities to be fulfilled [6], they are commonly still divided in three main dominia suggested primarily by Willner in 1984 [7]; these are construct, face, and predictive validity. In the herein focused predictive validity, animals should respond to well-documented treatments in clinical practice in a similar way as patients do. In this case, it means the reduction of depressive-like behaviors. Taking all this into account, in this systematic review and meta-analysis, the consistency of the predictive validity of animal models of MDD will be tested through the evaluation of the behavioral responses of those models to a variety of pharmacological treatments. | |
| | Research question | | |
| 11. | Specify the disease/health problem of interest | Major depressive disorder | |
| 12. | Specify the population/species studied | Major depressive disorder / depression-like rat and mouse models | |
| 13. | Specify the intervention/exposure | Any drug or pharmacological agent | |
| 14. | Specify the control population | No treatment, vehicle, saline, or a second drug intervention. | |
| 15. | Specify the outcome measures | All behavioral and memory tests performed in both groups | |
| 16. | State your research question (based on items 11-15) | What are the behavioral and memory effects of pharmacological treatments in rat and mouse animal models of depression? | |
| | C. Methods | | |
| | Search and study identification | | |
| 17. | Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science) | ✓ MEDLINE via PubMed ✓ Web of Science<br>✓ SCOPUS ☐ EMBASE<br>☐ Other, namely:<br>☐ Specific journal(s), namely: | |

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| 18. | Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21]) | Panzenhagen_supp_file_search_strategies.pdf | |
| 19. | Identify other sources for study identification | ✓ Reference lists of included studies ☐ Books<br>☐ Reference lists of relevant reviews<br>☐ Conference proceedings, namely:<br>☐ Contacting authors/ organisations, namely:<br>☐ Other, namely: | |
| 20. | Define search strategy for these other sources | - | |
| | Study selection | | |
| 21. | Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both) | 1) pre-screening based on title and abstract<br>2) full-text screening of the eligible articles | |
| 22. | Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved | a) at least 4 trained undergraduate independent reviewers in phase 1 and 2 post-graduate/professors independent reviewers in phase 2. At least three agreeing classifications in phase 1 and 100% agreement in phase 2 were considered.<br>b) discrepancies will be resolved by discussion with a fifth (phase 1) or third (phase 2) reviewer. | |
| | *Define all inclusion and exclusion criteria based on:* | | |
| 23. | Type of study (design) | Inclusion criteria: Any type of study design is of interest<br>Exclusion criteria: None | |
| 24. | Type of animals/population (*e.g.* age, gender, disease model) | Inclusion criteria: The following rat or mouse models of depression: olfactory bulbectomy, chronic unpredictable mild stress, chronic mild stress, mild stress, acute stress, social defeat, learned helplessness, and restrain stress. All age and gender groups will be included.<br>Exclusion criteria: Studies that do not include at least of the animal models cited above. | |
| 25. | Type of intervention (*e.g.* dosage, timing, frequency) | Inclusion criteria: Any pharmacological intervention, added or not by a second pharmacological intervention.<br>Exclusion criteria: Studies that do not include pharmacological interventions or only have groups in which the pharmacological intervention is added by a non-pharmacological intervention. | |
| 26. | Outcome measures | Inclusion criteria: Behavioral or memory test outcomes.<br>Exclusion criteria: Studies that do not perform behavioral ou memory tests in the model/intervention groups included. | |
| 27. | Language restrictions | Inclusion criteria: All languages<br>Exclusion criteria: None | |
| 28. | Publication date restrictions | Inclusion criteria: All publication dates<br>Exclusion criteria: None | |
| 29. | Other | Inclusion criteria: None<br>Exclusion criteria: None | |
| 30. | Sort and prioritize your exclusion criteria per selection phase | Selection phase 1:<br>1. Study is a review, letter, or commentary<br>2. Study does not include rats or mice<br>3. Study does not include one of the chosen models | |

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| | | 4. Study does not include any pharmacological intervention<br>5. Study does not include a second group with no treatment, vehicle, or intervention with another drug.<br>6. Study does not perform any type of behavioral or memory test with all included experimental groups<br><br>Selection phase 2:<br>1. Study is a review, letter, or commentary<br>2. Study does not include rats or mice<br>3. Study does not include one of the chosen models<br>4. Study does not include any pharmacological intervention<br>5. Study does not include a second group with no treatment, vehicle, or intervention with another drug.<br>6. Study does not perform any type of behavioral or memory test with all included experimental groups | |
| | Study characteristics to be extracted (for assessment of external validity, reporting quality) | | |
| 31. | Study ID (*e.g.* authors, year) | First author, year of publication, journal name, DOI. | |
| 32. | Study design characteristics (*e.g.* experimental groups, number of animals) | Experimental groups, sample sizes. | |
| 33. | Animal model characteristics (*e.g.* species, gender, disease induction) | Species, gender, type of disease induction, age of the animal upon induction and outcome assessment. | |
| 34. | Intervention characteristics (*e.g.* intervention, timing, duration) | Type of intervention, dosage, timing, duration, route of administration. | |
| 35. | Outcome measures | Mean, standard deviation (SD) by group and sample size. Or other effect measures and p-values when mean and SD are not available. | |
| 36. | Other (*e.g.* drop-outs) | | |
| | Assessment risk of bias (internal validity) or study quality | | |
| 37. | Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved | Two independent trained reviewers will assess the risk of bias assessment of each study. Discrepancies will be resolved by discussion between reviewers or assessment by a third reviewer when necessary. | |
| 38. | Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power) | ✓ By use of SYRCLE's Risk of Bias tool[4]<br>☐ By use of SYRCLE's Risk of Bias tool, adapted as follows:<br>☐ By use of CAMARADES' study quality checklist, e.g [22]<br>☐ By use of CAMARADES' study quality checklist, adapted as follows:<br>☐ Other criteria, namely: | |
| | Collection of outcome data | | |
| 39. | For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement) | Mean or median and standard deviation or interquartile interval when continuous and incidence/percentage in each group when dichotomous outcomes of all behavioral and memory tests applied in the original records. | |
| 40. | Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors) | First extraction from text and tables, then from graphs and figures using WebPlotDigitizer v 4.3. When the information required in not available, the authors of original studies will be contacted. If no answer is received in two months the records will be excluded from the analysis. | |

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| 41. | Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved | a) All data will be extracted independently by two reviewers. b) Discrepancies will be resolved by a third reviewer data extraction. | |
| | Data analysis/synthesis | | |
| 42. | Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis) | For all outcome measures the descriptive summary and effect sizes will be compared qualitatively. A meta-analysis will be conducted whenever is possible according to the criteria below. | |
| 43. | Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed | A meta-analysis will be performed whenever there are at least three studies with the same design reporting data for the same animal model, drug, comparison group, and type of behavioral or memory test. | |
| | *If a meta-analysis seems feasible/sensible, specify (for each outcome measure):* | | |
| 44. | The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio) | Standardised mean difference and odds or risk ratios when the first is not a possibility. | |
| 45. | The statistical model of analysis (*e.g.* random or fixed effects model) | A random effects model will be used in order to account for heterogeneity. | |
| 46. | The statistical methods to assess heterogeneity (*e.g.* $I^2$, Q) | $I^2$ and Cochran Q statistics | |
| 47. | Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis) | Subgroup meta-analyses (meta-regression or stratified regression) according to the following potential heterogeneity introducing variables: species, strain, sex, drug delivery route, drug dosage, age and/or weight of animals. | |
| 48. | Any sensitivity analyses you propose to perform | Sensitivity analyses will be performed as follows: a) following the Jackknife method for all main meta-analysis groups. b) according to risk of bias quality score of original studies (poorly classified studies in the 25% bottom quartile will be excluded). c) in case of doubts regarding the assumptions and interpretation of previous analyses. | |
| 49. | Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group) | Bonferroni post hoc analysis will be conducted according to the number of tests performed. Whenever one control is used multiple times the number will be adjusted by dividing the total sample size by the number of times that group is included in the analysis.<br>Additionally, study and research group (same last author) will be included as an additional random variable to account for neglected heterogeneity. A network meta-analysis will also be performed including all drugs in each model. | |
| 50. | The method for assessment of publication bias | Funnel plotting and Egger's regression test. | |
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| Final approval by (names, affiliations): | | Date: | |

**References**


1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7
2. Greenberg PE, Fournier A-A, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76(2):155-162. doi:10.4088/JCP.14m09298
3. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905
4. van der Staay FJ, Arndt SS, Nordquist RE. Evaluation of animal models of neurobehavioral disorders. *Behav Brain Funct*. 2009;5:11. doi:10.1186/1744-9081-5-11
5. Ramaker MJ, Dulawa SC. Identifying fast-onset antidepressants using rodent models. *Mol Psychiatry*. 2017;22(5):656-665. doi:10.1038/mp.2017.36
6. Belzung C, Lemoine M. Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biol Mood Anxiety Disord*. 2011;1(1):9. doi:10.1186/2045-5380-1-9
7. Willner P. The validity of animal models of depression. *Psychopharmacology (Berl)*. 1984;83(1):1-16. doi:10.1007/BF00427414