Evaluating Construct Validity within Preclinical *In Vivo* Animal Research

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Glossary

CV – Construct Validity

DistillerSR - Distiller Systematic Review

ICD-10 – International Classification of Disease – 10

PRESS – Peer Review of Electronic Search Strategy

PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analyses

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Abstract

Background: Construct validity refers to the degree to which tests that claim to measure a "*construct*" (i.e., an inferred concept that is intangible regarding an individual's health or internal state such as a disease, or postulated attribute) are truly reflective of that specific construct. It is suggested that construct validity is an important concept in preclinical research, as it may help reduce misinterpretations of study results allowing for better ability to predict the success of clinical translation of preclinical studies. However, there is a lack of empirical evidence to confirm its impact on preclinical research efficacy.

Objectives: (I) Conduct a scoping review of the construct validity literature as it relates to the design of *in vivo* animal studies. (II) Conduct an overview of systematics reviews evaluating the application and reporting of construct validity within systematic reviews of *in vivo* animal studies.

Methods: For the scoping review, we searched Embase, MEDLINE, and Google Scholar. Eligibility criteria was intentionally broad as we included any article that mentioned construct validity in preclinical *in vivo* research. Further review of citations was performed on eligible studies that provided substantial discussion on construct validity. For the overview, we searched MEDLINE, Embase, and TOXLINE for systematic reviews of preclinical *in vivo* interventions. The outcomes of interest were the prevalence of systematic reviews that mentioned construct validity and the prevalence of reviews that assessed construct validity.

Results: The literature searches for the scoping and overview yielded 3657 and 2356 articles, respectively. After screening 372 and 444 met inclusion criteria for the scoping and overview. Six codes were generated (theory; mechanism; matches the human condition; measures what it reports to; experimental conditions; and outcomes) from the content analysis for the definition of

construct validity. Of the 444 systematic reviews, seven mentioned construct validity, but only three used the term construct validity directly. None of the systematic reviews assessed construct validity.

Discussion/Conclusion: Construct validity was not defined uniformly among studies suggesting it is not clearly understood. There was limited reporting on construct validity in systematic reviews and entirely no assessment of it; this may reflect a lack of awareness of this concept. Future research should aim to find a consensus on the definition of construct validity in order to develop tools and frameworks to help researchers assess construct validity.

Keywords: construct validity, validity, preclinical, in vivo, scoping review, overview of systematic reviews.

Chapter 1. Introduction

Background

The concept of validity is generally well-established within health research (Long & Johnson, 2000). Validity refers to the extent that model or experimental measures can be generalized and truly reflects the phenomenon they are claiming to represent (Bailoo, Reichlin, & Wurbel, 2014). The concept of validity can be split into more specific types of validity and some examples of these are internal, external and construct validity. *Internal validity* refers to how the study design and conduct impact the risk of bias, so that causal inferences from an experimental intervention on change in an outcome measure is justified (Bailoo et al., 2014). *External validity* refers to the generalizability of conclusions about causal relationships from one population, setting and time onto other populations, settings, and times (Shadish, Cook, & Campbell, 2002).

Construct validity is a more complex and often confusing concept to researchers. It is not as commonly addressed or appraised as internal and external validity. Construct validity was first introduced in research by Meehl and Cronbach in 1955 (Cronbach & Meehl, 1955). They defined construct validity in terms of psychological test evaluation. In their definition, construct validity refers to whether the measures of the test reflect the general construct being measured. In this definition, a construct is either the concept, disease, or postulated attribute that is assumed to be reflected in the test (Cronbach & Meehl, 1955). If a researcher was studying depression, that clinical phenomenon would be considered as the construct and the researcher would evaluate construct validity by the measures chosen to reflect depression. Since this is the original definition of construct validity and has been used frequently in the field of psychology it will be used as the primary definition in this thesis.

Recently, an adaptation of the first definition of construct validity has gained popularity among preclinical researchers (Henderson, Kimmelman, Fergusson, Grimshaw, & Hackam, 2013). Within this context, preclinical research includes laboratory experiments that use animals or nonhuman cells. Their adapted definition of construct validity refers to the degree to which interpretations from a particular experiment can be acceptably made from an evaluation of experimental characteristics to the target they are intended to represent (Henderson et al., 2013). In more general terms for biomedical research, construct validity asks how well the chosen "constructs" in the experiment do truly emulate the clinical disease and characteristics it is designed to represent. In this definition a construct can be either the phenomenon (depression) like in the primary definition or it can refer to a unit included in an experiment, such as animals/cells, treatments, models, outcomes, and settings (Shadish et al., 2002).

Not only has construct validity been defined differently, but it also often gets confused or combined under the same umbrella as external validity in preclinical research (Henderson et al., 2013). These two concepts are related to generalization; however, external validity applies the context of a study to other settings and environments whereas construct validity looks to generalize the concept of measures to the clinical attribute it is intended to replicate (Trochim, 2007). As an illustrative example, if a researcher has investigated a novel therapy in a murine model of Alzheimer's disease, an assessment of the study results' ability to be replicated in different animal models, ages, or species is an assessment of external validity. If the researcher is seeking to establish whether the animal model is reflective of the "*construct*" Alzheimer's disease, they must assess the correlation or degree to which the model represents the clinical phenomenon in question; this would be an assessment of construct validity. External and

construct validity can be used to verify the relevance of the preclinical animal model (Pound & Ritskes-Hoitinga, 2018; Yanagi, Southcott, Lister, & Tamminga, 2012).

The degree to which some experimental factors (e.g. type of animal model, biological sex, or severity of the model) represent the construct of interest can vary widely. For example, given the similarities between swine and human cardiac anatomy and physiology, a pig model of cardiac ischemia-reperfusion might allow for a better representation of human myocardial infarction than a mouse model. In contrast, construct validity can be threatened by a number of factors. It has been suggested that preclinical researchers can hinder construct validity by choosing measures and outcomes that are not clinically relevant or representative of the clinical phenomenon (Henderson et al., 2013). The impact of one or more threats to validity can impact the ability to interpret study results. An example of a threat to construct validity is choosing to use male animals when the clinical disease, such as breast cancer, is predominantly prevalent in females. These mischaracterizations of the relationship between preclinical to clinical settings may lead to failure of carrying over to clinical trials (Kimmelman & Henderson, 2016). Hence, it has been suggested that experimental conditions should be evaluated critically to ensure the adequacy of these experimental choices (Leary-Kelly & J. Vokurka, 1998).

Thesis Rationale

Although many researchers have suggested that construct validity may be an important concept in preclinical research, there is a lack of empirical evidence and comprehensive evaluation of the existing literature on the topic. Since preclinical research directly informs clinical research (e.g., the development of novel therapeutics), a better understanding of this validity may ultimately improve translation of preclinical findings to the clinical context. Careful consideration of construct validity as a preclinical study is designed and executed may

prevent misinterpretation of results; ultimately, this may help ensure the models and measures chosen by the researchers reflect the intended construct they wish to measure and better inform downstream translation to clinical contexts (Trochim, 2007). In order to support and improve future consideration of construct validity in preclinical laboratory research, a comprehensive summary of the existing literature on this concept is first needed. Therefore, the aim of this thesis is to understand the use and discussion of construct validity in preclinical *in vivo* animal research. Specifically, we wish to determine the prevalence and extent of assessment in preclinical *in vivo* animal research.

Objectives

The two objectives of this thesis are as follows: *(I) Conduct a scoping review of the construct validity literature as it relates to the design of in vivo animal studies.* The scoping review will provide an evidence map and identify the gaps from the existing published literature around construct validity of preclinical *in vivo* animal models. *(II) Conduct an overview of systematic reviews evaluating the application and reporting of construct validity within published systematic reviews of in vivo animal studies.* The purpose of this review is to determine the prevalence of preclinical systematic reviews that evaluate construct validity and how it is analyzed.

Structure of Thesis

Chapter 1 of this thesis provides a background on the thesis topic, the rationale, and states the objectives. This thesis includes two protocols and two manuscripts. Chapters 2 and 4 describe the protocols for the scoping review and overview of systematic reviews, respectively. Both have been registered on the Open Science Framework. Chapters 3 and 5 summarize the results of both reviews. Chapter 6 discusses the implications of the results obtained.

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Chapter 2. Scoping Review of Construct Validity of Preclinical Animal Studies in Current Literature: Protocol

Preface:

This chapter outlines the protocol the scoping review we conducted. The protocol was registered on Open Science Framework and updated with amendments as per usual scoping review methods. Rania Berjawi initially drafted the protocol, co-developed the search strategy with a librarian (Risa Shorr, MLS), and created data extraction forms. Sascha Davis performed a Peer Review of Electronic Search Strategy (PRESS) review. Drs. Fergusson, Lalu, and Brehaut provide input on all components following initial drafting. The authors listed also supervised to the development of the eligibility criteria and data extraction forms. All authors approved the final protocol.

Protocol Registration: Berjawi, R., Lalu, M. M., Brehaut, J., & Ferguson, D. (2020, September 13). Construct Validity of Preclinical Animal Studies: A Scoping Review. https://doi.org/10.17605/OSF.IO/YUQF9

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Background

Construct validity is a concept that was first introduced in psychological research by Meehl and Cronbach in 1955 to evaluate psychometric tests (Cronbach & Meehl, 1955). Their definition of construct validity refers to whether the measures of the test reflect the general construct being measured. In this definition, a construct is either the concept, disease, or postulated attribute that is assumed to be reflected in the test (Cronbach & Meehl, 1955). Construct validity outside of psychological research is not uniformly defined but may play an important role in the evaluation of preclinical animal research.

Currently, preclinical research focuses on other forms of validity when interpreting results of studies, such as internal and external validity, however construct validity has yet to be well defined. Proper evaluation of construct validity may prevent mislabeling and misinterpretation of preclinical study results by considering whether the measures chosen by the researchers reflect the intended construct they wish to measure (Trochim, 2007). Evaluating different types of validity in preclinical animal models may help researchers predict the efficacy of treatments in clinical settings. To properly assess the impact of construct validity there is a need for a comprehensive summary of the existing literature using the concept in preclinical research, so that it may be better understood.

To better understand how to define, apply and evaluate construct validity, there is a need for a scoping review to help synthesize the very expansive preclinical literature. The scoping review will provide a better understanding of how researchers are defining construct validity in preclinical research. Moreover, this review will help outline empirical evidence in the literature to assess the importance of construct validity in preclinical research. The information from this

review is necessary to enable future research on construct validity and assist evaluations of this concept in preclinical research.

Rationale

There is a lack of uniformity around the concept of construct validity in the area of preclinical research. There is no current review that summarizes, how the term construct validity is being used, the prevalence, and the extent to which researchers are discussing this concept as it pertains to preclinical research. A scoping review to map and characterize the concept of construct validity in the existing literature is required.

Objective

The objective of this review is to summarize the existing literature on construct validity as it relates to the design of preclinical animal studies and identify gaps pertaining to this concept within preclinical research.

Methods

Protocol

The scoping review protocol will follow five steps outlined by Arksey & O'Malley and recommendations made by Levac *et al.* (Arksey & O'Malley, 2005; Levac, Colquhoun, & O'Brien, 2010). The steps are as follows (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting data, and (5) collating, summarizing and reporting the results. The results of this scoping review will be reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis – Scoping Review guidelines (PRIMSA-ScR) (Tricco et al., 2018).

Identifying the Research Question

The research question for this scoping review is: ***"How is construct validity being defined and used in preclinical animal research literature?"*** The research question aims to

identify all relevant published literature that discusses construct validity in preclinical research. This will provide an overview of how the concept is being defined and applied in the field of preclinical research. It will also provide an overview of how the definition of construct validity has evolved to the definition stated above. It will also identify whether the terminology is being used appropriately and distinctly from external validity definitions.

Identifying Relevant Studies

Studies will be identified by searching electronic databases and reference lists of included studies. The searches will be conducted on Embase, Ovid (MEDLINE), and Google Scholar in consultation with an information specialist. A second information specialist will conduct a second peer review of the search strategy using the PRESS checklist (McGowan et al., 2016). There is no general guidance around how many records to screen from a Google Scholar search, but typically systematic reviews screen the first 50 to 100 records (5 to 10 pages) (Haddaway, Collins, Coughlin, & Kirk, 2015). For the purpose of our scoping review, we will be conservative and screen the first 100 records; in order to avoid personalization of search results, the 'private browser' mode will be used in Google Chrome. Furthermore, citation searching will be performed on the included studies that have substantial discussion of construct validity to find relevant articles the search may have missed. Citation searching will be performed in forward and backward searching. This search will be done by searching through the reference list (backward) and looking at the texts that cited the included papers (forward) (Hinde & Spackman, 2015). The search will be refined as needed during screening, which will be conducted by two independent reviewers. There will be no language or date restriction. Key terms that will be in the search include *construct, external, predictive, animal, in vivo, preclinical, and experimental.*

Study Selection

During the study selection process reviewers will focus on identifying whether the studies discuss, characterize or describe construct validity, specifically in the context of preclinical *in vivo* animal research. Studies will be evaluated for relevance, whether it answers the research question or not. Inclusion criteria are defined as published literature, such as primary studies, narrative reviews, reports, textbooks, commentaries, and editorials that provide description, discussion and/or characterization of construct validity in the domain of preclinical *in vivo* animal research. Studies will be excluded if they only mention construct validity, but do not provide a description, discussion, or characterization of construct validity. Studies that discuss construct validity in terms of psychometric testing will be excluded due to feasibility. Only studies in English text will be considered due to translation difficulties of such an abstract concept. There will be no date restriction in the search. The study selection process will be iterative, in which the search strategy will be refined when appropriate to ensure the best possible search. As familiarity with the literature increases inclusion and exclusion criteria will be further refined.

Distiller Systematic Review Software (DistillerSR) (Evidence Partners, Ottawa, Canada), a cloud-based program will be used to upload, manage, and screen the results from the literature review. Results from EMBASE and Medline will be screened first by title/abstracts before moving onto full-text screening. The results from the Google Scholar search will be screened by titles and then by full text. As recommended by Levac both reviewers will meet at the beginning, midpoint, and final stages of abstract screening to discuss any issues or challenges and refine the search strategy as needed (Levac et al., 2010). To reduce time required to screen titles and abstracts a 'liberal accelerated' screening method will be used. In this method a second independent reviewer will screen the list of excluded studies from the first reviewer and studies

that the first reviewer includes will move directly to full text screening (Tricco et al., 2015). During abstract/title screening studies will be included if they include the terms construct, external, or predictive validity, "types of validity", or "validity types", clinical inference, and translational research along with the other inclusion criteria stated above. At full text screening the articles that include only the term external validity they must define it using concepts similar to construct validity to be included, otherwise it will be excluded. Reasons for exclusion will be documented at the full-text stage. Any conflicts will be resolved through discussion or by a third member. Reference lists of included studies will be checked for any additional studies that may be relevant to the review.

Charting Data

Data extraction forms will be created on DistillerSR and extraction will be performed in duplicate; conflicts will be resolved through discussion or by a third member. In order to chart the data an iterative process will be followed in which a pilot of five to ten studies will be extracted using pre-established data charts, however, these charts can be updated as the extraction process is carried out (Levac et al., 2010). Items to extract will include *author; year of publication; country; type of published literature/study; purpose/target field for construct validity; animal population or model.* Outcomes to extract include *definition of construct validity; importance/relevance to preclinical research; key characteristics of construct validity; evidence/support for construct validity discussion/characteristics.* We will extract quotes or summarize discussion authors have used to state the importance/ relevance to preclinical research.

Collating, Summarizing, and Reporting the Results

Results will be exported into a Microsoft Excel spreadsheet to create tables. Extracted data will be summarized both quantitatively and qualitatively. Study characteristics will be presented descriptively and quantitatively as frequencies. To organize the data extracted for key characteristics and the definitions of construct validity provided by the included studies a conventional content analysis will be performed. This approach is used to describe a phenomenon when there is either no existing theory or limited theory on the phenomenon (Hsieh & Shannon, 2005). Steps of a content analysis begin by familiarizing yourself with the data by reading and rereading the data to derive codes from key initial thoughts. The codes are then sorted into categories to organize them into meaningful clusters and definitions for each category and subcategory are developed. A separate list of recommendations for evaluating construct validity will be created. Recommendations will be ranked by how frequently recommended each item is by authors in the included studies.

Discussion and Dissemination

The results of this scoping review will help identify the various definitions of construct validity and how it is being applied in preclinical research. This comprehensive summary of the literature of construct validity can provide researchers better understanding of construct validity. Furthermore, the recommendation items extracted from this scoping review will be used in the future to develop a list of key recommendations for the assessment of construct validity, through a consensus exercise with experts in the field of preclinical and validity research. The results of the scoping review will be collated into a manuscript for future publication.

Amendments from Version 1 of Protocol:

I. In version one of the scoping review protocol citation searching was to be performed on all of the included studies. However, due to the large amount of studies that were found to meet the inclusion criteria, citation searching on all of them was not feasible. Therefore, we decided that citation searching will only be performed on the included studies that have substantial discussion of construct validity (i.e., greater than 10 sentences on construct validity) to find relevant articles the search may have missed.

II. Studies that discuss construct validity in terms of psychometric testing will be excluded due to feasibility. This exclusion criteria was added because psychometric testing was out of the scope with our study due to the extensive time that would be needed to review the immense number of articles on psychometric testing.

III. In version one of the protocol two independent reviewers were set to screen titles and abstracts. However, to reduce time required to screen titles and abstracts a 'liberal accelerated' screening method will be used. In this method a second independent reviewer will screen the list of excluded studies from the first reviewer and studies that the first reviewer includes will move directly to full text screening (Tricco et al., 2015).

IV. At full text screening the articles that include only the term external validity they must define it as construct validity to be included otherwise it will be excluded. This exclusion criteria was added to help determine whether external validity was being misinterpreted as construct validity.

V. For the definitions of construct validity identified we will be doing a content analysis. The steps of a content analysis begin by familiarizing yourself with the data by reading and rereading the data to derive codes based off of key initial thoughts (Hsieh & Shannon, 2005). The codes are then sorted into categories to organize the codes into

meaningful clusters and definitions for each category and subcategory are developed (Hsieh & Shannon, 2005).

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Chapter 3. Scoping Review of Construct Validity of Preclinical Animal Studies in Current Literature

Preface:

This chapter includes the manuscript and final results of the scoping review conducted in this thesis. This scoping review scanned the existing literature on construct validity in preclinical *in vivo* animal studies. The initial draft of this manuscript was drafted by Rania Berjawi and co-authors Drs. Fergusson, Lalu, and Brehaut provided revisions and edits. Visualizations were created and analyses were performed by Rania Berjawi. Drs. Fergusson, Lalu, and Brehaut provided supervision and feedback for the content analysis. All authors have read and approved the final manuscript. This manuscript has not been submitted for publication yet.

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Abstract

Background: Construct validity is an important consideration in the design and execution of preclinical *in vivo* animal research. However, construct validity is poorly understood, and it is unclear how researchers are defining this concept. Thus, a scoping review to map and characterize the concept of construct validity in the current literature is necessary.

Objective: The objective of this review is to summarize the existing literature on construct validity as it relates to the design of *in vivo* animal studies and identify gaps pertaining to this concept within preclinical research.

Methods: A literature search was performed on Embase and MEDLINE to identify articles that mention construct validity in preclinical *in vivo* animal research using key terms including construct, external, predictive, animal, *in vivo*, preclinical, experimental, model validity, and translational medical research. Google Scholar was searched for relevant articles and citation searching was also performed. A conventional content analysis was performed on the definitions of construct validity provided in the articles.

Results: A total of 3657 references were yielded from the searches and 372 articles matched our eligibility criteria. Publications ranged from 1984 to 2019 with the majority of articles focusing on mental and behavioural disorders. The content analysis resulted in six distinct categories researchers used to define construct validity. The categories involved elements such as theory; mechanism; model matches the human condition; measures what it reports to; experimental conditions; and outcomes.

Conclusion: The preclinical *in vivo* animal research community lacks uniformity on the definition of construct validity. Future studies are needed to help achieve a consensus definition for construct validity.

Background

Construct validity is a concept introduced in psychological research by Meehl and Cronbach in 1955 to evaluate psychometric tests (Cronbach & Meehl, 1955). Their definition of construct validity refers to whether the measures of the test validate the general construct being measured. In this definition, a construct is either the concept, disease, or postulated attribute that is assumed to be reflected in the test (Cronbach & Meehl, 1955). Construct validity, outside of psychological research has not been uniformly or extensively defined in the literature.

Currently, preclinical biomedical research has clear and consistent definitions for certain forms of validity when designing, executing, and interpreting results of studies, such as internal and external validity, however construct validity has yet to be well defined (Henderson et al., 2013). External validity is defined as the degree generalizations can be made from one population, setting, or time onto another population setting or time (Pound & Ritskes-Hoitinga, 2018). Several researchers define external validity and construct validity as the same or similar concept; however, others see them as distinct concepts, these differences make it difficult to evaluate construct validity (Henderson et al., 2013)

Construct validity may play an important role in the evaluation of preclinical animal research. Therefore, the proper evaluation of construct validity in research studies may help improve the understanding and implication of study results by considering whether the measures chosen by the researchers truly reflect the intended construct(s) they wish to measure (Trochim, 2007). Evaluating different types of validity in preclinical animal models may help researchers predict the efficacy of treatments in clinical settings. To properly assess the impact of construct validity there is a need for a comprehensive summary of the existing literature around the concept in preclinical research, so that we may better comprehend all the elements of construct

validity. Researchers should address construct validity during experimental design by ensuring the animal model they have chosen mimics the human condition, or the outcomes chosen are clinically relevant (Kimmelman & Henderson, 2016).

To advance the area of biomedical animal research and understand how to evaluate construct validity there is a need for a broad synthesis of the preclinical *in vivo* research literature pertaining to this concept. This scoping review will provide an understanding of how researchers are defining construct validity in preclinical research. Additionally, we wish to help enable future research on construct validity and determine if there is a need to develop a consensus definition of construct validity as a step forward to understanding how to properly evaluate the concept in preclinical research.

There is no current review that summarizes, how the term construct validity is being used, the prevalence, and the extent to which researchers are discussing this concept as it pertains to preclinical research. Due to the limited research present on construct validity, a scoping review would be the most appropriate starting point. Scoping reviews allow for a broad scan of the literature, which is helpful when you have limited knowledge or previous reviews done on the subject beforehand. Therefore, a scoping review to map and characterize the concept of construct validity in the existing literature is warranted. The specific objective of this review is to summarize the existing literature on construct validity as it relates to the design of *in vivo* animal studies and identify gaps in the understanding and terminology pertaining to this concept within preclinical research.

Methods

The protocol for this review was registered on Open Science Framework (https://doi.org/10.17605/OSF.IO/YUQF9). It is reported in accordance with Preferred Reporting

Items for Systematic Reviews and Meta-Analysis Scoping Review Extension (PRISMA-ScR), completed checklist in Appendix E. This scoping review followed the five steps outlined by Arksey & O'Malley and recommendations made by Levac et al. (Arksey & O'Malley, 2005; Levac et al., 2010). The steps were (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting data, and (5) collating, summarizing and reporting the results.

Research Question

The research question for this scoping review was: "***How is construct validity being defined and used in preclinical animal research literature?"*** The research question aimed to summarize all relevant published literature that discusses construct validity in preclinical research. This will provide an overview of how the concept was defined and applied in the field of preclinical research. It will also provide an outline of how the definition of construct validity by Cronbach and Meehl has evolved to the definition by Henderson et al. We also wanted to identify whether the terminology was being used appropriately and distinctly from external validity definitions, since several researchers assert that they are the same concept.

Identifying Relevant Studies

Studies were identified by searching electronic databases and reference lists of included studies. A systematic search strategy was applied to Embase, Ovid (MEDLINE) on October 10th, 2019 with an information specialist. A second information specialist conducted a peer review of the search strategy using the PRESS checklist (McGowan et al., 2016). There was no language or date restriction. Key terms that were in the search included construct, external, predictive, animal, *in vivo*, preclinical, experimental, model validity, and translational medical research. The complete search strategies and PRESS review can be found in Appendix C. Additionally, Google

Scholar was searched twice with different term combinations on April 29, 2020 and April 30, 2020. The first 100 records were screened for each on 'private browser' mode in Google Chrome. Keyword searches imputed into Google Scholar were "construct validity" and "animal experiments" and the second search included "construct validity" and "preclinical". Furthermore, forward and backward citation searching was performed on the included studies focused on construct validity or there was substantial discussion of construct validity (i.e., more than 10 sentences about construct validity) (Hinde & Spackman, 2015).

Selecting Studies

During the study selection process reviewers focused on identifying articles that discussed, characterized or described construct validity, specifically in the context of preclinical *in vivo* animal research. Inclusion criteria were defined as published literature, such as primary studies, narrative reviews, reports, textbooks, commentaries, and editorials that provide description, discussion and/or characterization of construct validity in the domain of preclinical *in vivo* animal research. Studies were excluded if they only mention construct validity, but do not provide a description, discussion, or characterization of construct validity. Studies that discuss construct validity in terms of psychometric testing were excluded because they were out of the scope with our study due to the extensive time that would be needed to review the immense number of articles on psychometric testing. Only studies in English text were considered due to expected translation and interpretation difficulties. There were no date restrictions.

Charting Data

Distiller Systematic Review Software (DistillerSR) (Evidence Partners, Ottawa, Canada), a cloud-based program was used to upload, manage, and screen the results from the literature review. Results from Embase and MEDLINE were screened first by title/abstracts before moving

onto full-text screening. The results from the Google Scholar search were screened by titles and then by full text. To reduce time required to screen titles and abstracts a 'liberal accelerated' screening method was used. In this method a second independent reviewer screened the list of excluded studies from the first reviewer and studies that the first reviewer includes moved directly to full text screening (Tricco et al., 2015). During abstract/title screening, studies were included if they included the terms construct, external, or predictive validity, "types of validity", or "validity types", clinical inference, and translational research along with the other inclusion criteria stated above. At full text screening the articles that included only the term 'external validity' had to define it in accordance to the definitions of construct validity by Cronbach & Meehl or Henderson et al (Cronbach & Meehl, 1955; Henderson et al., 2013). Reasons for exclusion were documented at the full text stage. Any conflicts were resolved through discussion or by a third member.

Collating, Summarizing, and Reporting the Results

Data extraction forms were created on DistillerSR and extraction was performed in duplicate; any conflicts were resolved through discussion or by a third member. Items to extract included: author; year of publication; country; journal; type of published literature/study; medical classification; animal species and model. Articles were categorized by medical classifications using the International Statistical Classification of Disease (ICD) – 10. The dedicated article space given to construct validity was categorized into the following five categories: term only, 1-3 sentences, 4-10 sentences, more than 10 sentences, and 'did not mention'. Outcomes extracted include definition of construct validity; importance/relevance to preclinical research according to the researcher; key characteristics of construct validity; factors

that hinder/ improve construct validity. We extracted quotes or summarized discussion authors had used to state the importance/ relevance to preclinical research.

Results were exported into Microsoft Excel spreadsheet to create tables. Study characteristics were presented descriptively and quantitatively as frequencies. A conventional content analysis was performed in order to organize the data extracted for key characteristics and the definitions of construct validity provided by the included studies. This is an inductive approach that is specifically used to describe a phenomenon when there is no existing or limited theory on the phenomenon (Hsieh & Shannon, 2005). Since research on construct validity is limited there was no framework to start with, so a conventional content analysis was most appropriate. Steps undertaken for the content analysis included familiarizing ourselves with the data by reading and rereading the data to derive codes based off of key initial thoughts (Hsieh & Shannon, 2005). The codes were reviewed by two other reviewers to help reduce subjectivity of the process and amendments were made to the codes if necessary. The codes were then collated together if they were similar to one another (Hsieh & Shannon, 2005). The frequency of each category was recorded for each of the articles that defined construct validity. A codebook was created to define each code for transparency and objectivity.

Results

A total of 3622 references were identified from the Embase and MEDLINE search, and an additional 19 references found through the Google Scholar (16 references) and the citation searching (three references). After screening, a total of 372 articles met our eligibility criteria for this review, which has been summarized in Figure 1 in Appendix B.

Study Characteristics

The years of publication ranged from 1984 to 2019 and the top three countries of residence of corresponding authors were, the USA (n =126, 34%), followed by the UK (n=30, 8%), and Canada (n=26, 7%). The majority of articles were focused on mental and behavioural disorders (n=278, 75%). The types of articles included reviews (n=191, 51%), original research articles (n=127, 34%), chapters (n=18, 5%), reports or letters (n=17, 5%), editorials or commentaries (n=7, 2%), systematic reviews (n=9, 2%), and protocols (n=3, 1%). Other data collected on individual study characteristics is summarized in Table 1 in Appendix A and summary data is provided in Table 2 Appendix A.

Construct Validity Characteristics

Summary of construct validity characteristics of the included studies is provided in Table 3 Appendix A. Sixty percent of the articles (n=225) provided a definition of construct validity and 34% of articles (n=126) provided a citation for a construct validity definition. Construct validity was commonly mentioned in the abstracts (n=271, 73%) of the included articles and least mentioned in the results section (n=9, 2%) of the articles. The dedicated article space given to construct validity was term only (n=21, 6%); 1 – 3 sentences (n=174, 47%); 4 – 10 sentences (n=121, 32%); more than 10 sentences (n=55, 15%) this percentage also portrays whether construct validity was the main focus (i.e., >10 sentences) of the article. One article (0.3%) did not mention construct validity but defined external validity as construct validity. The majority of articles (n=290, 78%) did not discuss factors that may improve or hinder construct validity. Six percent (n=21) of articles also mentioned external validity, with 5% (n=1) defining external and construct validity as the same concept, 71% (n=15) defining them as separate concepts, 14% (n=3) stating there was overlap between the two definitions, and 10% (n=2) not providing a definition.

Content Analysis

Our conventional content analysis resulted in six distinct categories of construct validity definition elements, which are summarized in Table 5 in Appendix A. The categories generated were: choice of model supported by known theory; choice of model supported by known mechanism; choice of model needs to match the human condition; choice of outcome measure needs to match the human condition; experimental conditions need to represent the human condition; and the model measures what it reports to. Table 6 in Appendix A provides detail on how we further defined each of the categories with example quotes.

Choice of Model Needs to be Supported by a Known Mechanism

The code that appeared the most often (n=136) in the articles that defined construct validity was that the choice of the model needs to be supported by a known mechanism. This code was identified as any definition that takes into account the mechanism of action or cause of disease (physiology, chemistry, biology, genes, pathophysiology, etiology etc.). An example of a definition in one of the articles that would fall under this category would be, "The pathology should be triggered by events thought to be important in eliciting the human disorder and should involve similar neurochemical, neurobiological and psychobiological mechanisms" (Ciccocioppo, 2013). Elements in this definition that stood out in the content analysis were that the researcher stated that construct validity should take into account the pathology of the disease and it should reflect the various mechanisms of actions that the disease acts upon in the human condition.

Choice of Model needs to be Supported by a Known Theory

When doing the content analysis, we applied the code "choice of model needs to be supported by a known theory" to seventy-one articles defining construct validity. For this code to

be applied the definition of construct validity must have stated that construct validity is based on a proposed cause, theory, or underlying principle of disease. One example of a definition this code applied to was, “An approach designed to determine the degree to which an animal model incorporates relationships between multiple levels of analysis as proposed by theory” (Sarter, 2006). This definition states that theory needs to be accounted for when designing an animal model.

Choice of Model needs to match the human condition

Twenty-seven articles had the code “choice of model needs to match the human condition” applied to them. This code was defined as a definition referring to the preclinical model being chosen or justified by researchers to represent or recapitulate the clinical condition by matching the human condition to either the phenotype (symptomology/ features) or through similar behaviour changes, but does not discuss if it follows the same mechanism of action as the human condition. One definition that this code applied to was, “Construct validity implies that the cause of behavioral change in the animal is sufficient to cause a similar response in man” (Griebel, 1996). This definition suggests that the animal model has similar behavioural changes that match the human condition.

Model Measures What It Reports to

In the content analysis the code “model measures what it reports to” was applied to seventeen articles. This code was applied to definitions that were simplified and don't mention what part of the model researchers are interested in matching to the human condition, but rather the construct of interest. One example of this code that appeared in the content analysis was “Construct validity is how well a test measures what it reports to measure” (Commons, 2017).

This definition provided was limited in context, but simply stated that the test measures (i.e., model) is measuring what it intends to measure.

Experimental Conditions Need to Represent the Human Condition

The code "experimental conditions need to represent the human condition" was applied to thirteen of the articles defining construct validity. For this code the definition must suggest that construct validity is taken into account during aspects of experimental conditions such as designing and planning the experiment, models, outcomes, and other experimental measures are chosen or are justified by researchers to represent or recapitulate the clinical scenario and environment as a whole. An example of a definition this code applies to is, "Construct validity in preclinical research concerns the extent to which an experimental system accurately models a clinical entity" (Lalu, 2014). Here the researchers highlighted that construct validity relates to the experimental condition and how it reflects the human condition.

Choice of Outcome measure needs to match the human condition

The choice of outcome measure needs to match the human condition was least commonly used and only applied to eleven articles. This code was applied to definitions that referred to outcomes and endpoints being chosen or justified by researchers to represent or recapitulate the clinical condition. "Assessment of construct validity should be based on evidence about the level of agreement between the animal model, test or outcome variable and the quality it is meant to measure," was an example of a definition this code applied to (Wurbel, 2017). This definition includes outcome variables in the elements that impact construct validity.

Discussion

Our scoping review with a broad search of the published biomedical literature identified a total of 372 articles that mentioned construct validity within *in vivo* animal research. When we

normalized the data for year of publication and number of articles on construct validity within preclinical animal research, the number of articles has been increasing over time (Figure 2 Appendix B). However, even with this increase of publications that mention construct validity, the majority of these articles are mainly focused in mental and behavioural disorders, and nervous system disorders. Furthermore, the majority of the articles either only mentioned construct validity in less than three sentences or between four to ten sentences. The lack of attention to construct validity is concerning given its importance in ensuring optimizing the quality of an experiment and the potential in improving translation.

Construct validity was defined approximately half of the identified articles. There seems to be no single espoused definition for construct validity in preclinical *in vivo* animal research as the results of this review highlighted the variations in the definitions. The concept of construct validity had different key elements that were identified in the content analysis. There were six fairly distinct categories with "model needs to be supported by known mechanism" and "model needs to be supported by known theory" being the most common. Of the articles that were included in the content analysis (n=225), 60% of them that the mechanism of action is important to evaluate when looking at construct validity. This category was an interesting finding suggesting that many researchers believe that construct validity goes far beyond just the symptomology and outward appearance of the disease and rather it centres around the mechanism of disease and how it is mimicked in the animal model.

A few articles acknowledged the complexity of construct validity and multiple codes were applied to individual definitions in the content analysis. One example includes Peleg-Raibstein's (2012) definition, "In the context of animal models of human brain disorders, construct validity is a theory-driven, experimental substantiation of the behavioral,

pathophysiological, and/or neuronal elements of the model." This definition includes elements that pertain to theory and mechanism of disease. Moreover, one article cited six various definitions of construct validity in the literature (Belzung, 2011). Our review demonstrated that there is a lack of uniformity in what researchers believe constitutes as construct validity and that it is not homogeneous to either of the categories generated, but likely more intricate.

One theme that emerged in the content analyses suggested that experimental conditions need to be accounted for when considering construct validity. A scarce number of articles (n=13) acknowledged this notion. The idea of addressing construct validity in the design and planning of an experiment is important for researchers to focus on in order to maximize the translatability of their preclinical study results into clinical research (Pound & Ritskes-Hoitinga, 2018). Transparent reporting and discussion in original research studies does not often include discussion about construct validity of the experimental conditions chosen in the planning and design stage of experiments. In comparison, internal validity is included in the Animal Research: Reporting *In Vivo* Experiments (ARRIVE) guideline, which is a framework that guides researchers to provide transparent information on their study design (Percie du Sert et al., 2020). Authors are required to report on items that display the internal validity of their experimental design (Percie du Sert et al., 2020). Once the term construct validity is uniformly defined and properly understood, guidelines and tools can be created to aid researchers in evaluating and integrating the concept in their experiments.

When articles provided a reference for construct validity, many referenced one of three papers by one author (Table 4 Appendix A). These articles were written in the area of mental and behavioural disorders focusing on depression and anxiety disorders. These articles by Willner suggest that construct validity refers to the theoretical rationale of the disease (Willner, 1984,

1986). He suggests that construct validity of an animal model should be assessed through two specific criteria. The first criteria suggest that both the behaviour and the defining features of the model are unambiguously interpreted and homologous to the construct being studied (Willner, 1984, 1986). Furthermore, these conclusions about the behaviours and features being represented in the model should be made through sufficient understanding and knowledge of the construct (Willner, 1984, 1986). The second criteria stated that the level of change in the model needs to be essential to the disorder meaning (Willner, 1986).

A strength of this study was that a scoping review was the broad search that helped identify literature from a broad spectrum of *in vivo* animal research literature. Moreover, we performed multiple searches of databases and including citation searching to ensure we maximized our ability to capture as much of the literature on construct validity. However, one limitation to this study was with such a large scope we had to restrict using "validity" in our search terms, which may have resulted in missed articles. Quality of evidence was also not evaluated in this scoping review.

Conclusion

Our results suggest that construct validity is inadequately discussed, as more than half of the articles mentioned it in three or less sentences. Construct validity was understood differently among the preclinical literature and we identified six different categories in the content analyses. Future studies could consider performing a consensus exercise to help create a uniform definition of construct validity. Understanding how construct validity should be defined in all of its elements researchers can begin to generate checklists that provide researchers a tool to consider construct validity in the design of their own experiments, or the evaluation of this concept in work by others.

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Appendix A - Tables

Table 1. Individual Study Characteristics

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Mack (2019)	USA	Neuroscience and Biobehavioral Reviews	Review	Bipolar disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	0	4-10 sentences	Yes	N/A
Calabrese (2019)	USA	Pharmacological Research	Review	Huntington's Disease	Rodents	Transgenic and knockout	Abstract, Body of Text	0	In 1-3 sentences	No	N/A
Smarr (2019)	USA	Journal of Neuroscience Research	Original Research	Huntington's Disease	Mice	Knock-in model	Abstract	0	Term only	No	N/A
Depoortère (2019)	USA	Journal of Psychopharmacology	Original Research	Depression	Rats	Chronic stress model	Abstract, Introduction	0	In 1-3 sentences	No	N/A
Baba (2019)	Japan	Neuropsychopharmacology	Original Research	Psychiatric disorders	Mice	Knock-out Model	Abstract, Methods, Discussion	2	4-10 sentences	No	N/A
Sonnenschein (2019)	USA	Neuropharmacology	Review	Schizophrenia	Rats	Methylazoxymethanol acetate model	Introduction	1	In 1-3 sentences	Yes	N/A
Qin (2019)	China	Brain Research Bulletin	Review	Autism Spectrum Disorder	Macaque	Not specified	Abstract, Conclusion	1	In 1-3 sentences	Yes	N/A
Lena (2019)	France	Scientific Reports	Review	Autism Spectrum Disorder	Mice	Knock-out model	Abstract, Introduction	3	In 1-3 sentences	No	N/A
Dutta (2019)	USA	European Journal of Pharmacology	Original Research	Depression	Rats	Single prolonged stress model	Abstract	0	Term only	No	N/A
Jeanblanc (2019)	France	Neuroscience and Biobehavioral Reviews	Review	Addiction	Not specified	Not specified	Abstract, Conclusion	13	In 1-3 sentences	No	N/A
Post (2019)	Norway	Journal of Huntington's Disease	Original Research	Huntington's Disease	Mice	Knock-in model	Abstract	0	Term only	No	N/A
Veening-Griffioen (2019)	The Netherlands	European Journal of Pharmacology	Review	Alzheimer's disease	Not specified	Not specified	Introduction, Discussion	5	In 1-3 sentences	Yes	N/A
Smith (2019)	Australia	Brain, Behavior, and Immunity	Original Research	Post-traumatic stress disorder	Mice	Trauma exposure model	Abstract, Introduction	1	In 1-3 sentences	No	N/A
Giorgi (2019)	Italy	Frontiers in Behavioral Neuroscience	Review	Schizophrenia	Rats	Roman high- (RHA) and low-avoidance (RLA)	Abstract, Introduction, Body of Text	0	4-10 sentences	Yes	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Singh (2019)	India	Toxicology and Applied Pharmacology	Original Research	Psychosis	Mice	Neurodevelopmental model	Abstract, Introduction, Conclusion	0	In 1-3 sentences	No	N/A
Tadeven (2019)	USA	Mammalian Genome	Review	Not specified	Not specified	Not specified	Conclusion	0	10 or more sentences	Yes	N/A
Zorkina (2019)	Russia	Frontiers in Behavioral Neuroscience	Original Research	Depression	Mice	Chronic mild stress model	Abstract, Discussion	3	4-10 sentences	Yes	N/A
Silenieks (2019)	Canada	ACS Chemical Neuroscience	Original Research	Epilepsy	Rats	Selective 5-HT2C Agonists Model	Abstract, Discussion	3	In 1-3 sentences	No	N/A
Coleman (2019)	USA	Journal of Comparative Physiology	Original Research	Anxiety	Clawed frogs	Behavioural model	Abstract, Introduction, Discussion, Conclusion	1	4-10 sentences	No	Yes
Chadman (2019)	USA	Expert Opinion on Drug Discovery	Review	Autism Spectrum Disorder	Not specified	Not specified	Abstract, Body of Text	0	4-10 sentences	Yes	N/A
Topal (2019)	Hungary	Wiley's Interdisciplinary Reviews: Cognitive Science	Review	Autism Spectrum Disorder	Dog	Not specified	Abstract, Introduction, Body of Text	2	In 1-3 sentences	Yes	No
Hurel (2019)	France	Frontiers in Pharmacology	Original Research	Anorexia Nervosa	Mice	Activity based anorexia model	Abstract, Introduction	3	In 1-3 sentences	No	N/A
Broeck (2019)	Belgium	Frontiers in Behavioural Science	Original Research	Alzheimer's Disease	Mice	Not specified	Discussion	2	Term only	No	N/A
Faria (2019)	Spain	Nature	Original Research	Neurotoxic syndrome	Zebrafish	Acrylamide acute neurotoxicity model	Abstract, Body of Text	4	In 1-3 sentences	No	N/A
Maximino (2019)	The Netherlands	Behavioral and Brain Functions	Review	Not specified	Not specified	Not specified	Abstract, Body of Text, Conclusion	6	10 or more sentences	Yes	Yes
Ben-Ari (2019)	Israel	Brain research	Report	Vascular Dementia	Mice	Bilateral carotid artery stenosis	Abstract, Introduction, Discussion	1	In 1-3 sentences	No	N/A
Miguel (2019)	Brazil	Experimental Neurology	Original Research	Attention-Deficient Hyperactivity Disorder	Rats	Neonatal hypoxia-ischemia	Abstract, Introduction, Discussion	0	4-10 sentences	Yes	Yes
Hovath (2019)	Hungary	Physiology and Behaviour	Original Research	Schizophrenia	Rats	Wisket model	Introduction, Conclusion	1	In 1-3 sentences	No	N/A
Stutz (2019)	USA	Physiology and behavior	Review	Depression	Not specified	Not specified	Abstract, Introduction, Body of Text	2	4-10 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Caarazasta (2019)	Poland	Physiology and Behavior	Original Research	Depression	Rats	Chronic stress model	Abstract, Discussion	2	Term only	No	N/A
Hmeljak (2019)	Canada	Disease Models & Mechanisms	Editorial	Not specified	Not specified	Not specified	Introduction, Body of Text	3	4-10 sentences	Yes	No
Leffa (2019)	Brazil	Neuroscience and Biobehavioral Reviews	Systematic review	Attention-Deficient Hyperactivity Disorder	Rats	Not specified	Abstract, Introduction	7	In 1-3 sentences	Yes	No
Torok (2019)	Hungary	Progress in Neuropsychopharmacology & Biological Psychiatry	Review	Post-traumatic stress disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	10	4-10 sentences	Yes	Yes
Wendler (2019)	Brazil	Progress in Neuropsychopharmacology & Biological Psychiatry	Original Research	Mania	Rats	Not specified	Abstract, Introduction, Conclusion	4	In 1-3 sentences	No	N/A
Yao (2019)	China	Behavioural Brain Research	Original Research	Depression	Mice	Behavioural model	Abstract, Conclusion	0	In 1-3 sentences	No	N/A
Silva (2019)	Brazil	Psychology & Neuroscience	Review	Panic disorders	Not specified	Not specified	Abstract, Body of Text	0	4-10 sentences	Yes	Yes
Sena (2019)	UK	Animal Welfare	Review	Not specified	Not specified	Not specified	Abstract, Body of Text	1	4-10 sentences	Yes	No
Abi-Dargham (2019)	USA	Neuroscience and Biobehavioral Reviews	Review	Schizophrenia	Not specified	Not specified	Abstract, Introduction	3	Term only	No	N/A
Uilenreef (2019)	The Netherlands	Animals	Original Research	Osteoarthritis	Pigs	Naturally occurring model	Abstract, Introduction, Discussion	3	4-10 sentences	Yes	N/A
Valvassori (2019)	Brazil	Translational Psychiatry	Original Research	Bipolar disorder	Rats	Ouabain induced model	Introduction, Methods, Results, Discussion	3	10 or more sentences	Yes	Yes
Yezierski (2019)	Florida	The Journal of Pain	Review	Pain Disorders	Not specified	Not specified	Body of Text	29	In 1-3 sentences	Yes	No
Scott (2018)	Canada	The Journal of Neuroscience	Original Research	Autism Spectrum Disorder	Rats	Knock-out	Abstract, Introduction, Discussion	2	In 1-3 sentences	No	N/A
Laeken (2018)	Belgium	Journal of Neural Transmission	Original Research	Depression	Rats	Chronic unpredictable mild stress model	Abstract, Introduction, Discussion, Conclusion	5	4-10 sentences	Yes	Yes
Cenci (2018)	UK	Movement Disorders	Review	Parkinson's disease	Not specified	L-dopa-induced dyskinesia model	Abstract, Body of Text	19	4-10 sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Kostrzewa (2018)	USA	The Journal of Pharmacology and Experimental Therapeutics	Review	Psychiatric Disorders	Not specified	Not specified	Abstract	6	Term only	No	N/A
Hulbert (2018)	USA	Brain and Behavior	Original Research	Autism Spectrum Disorder	Mice	Knockout model	Abstract, Introduction	5	In 1-3 sentences	No	N/A
Pound (2018)	UK	Journal of Translational Medicine	Review	Not specified	Not specified	Not specified	Body of Text	22	In 1-3 sentences	Yes	No
Kovacevic (2018)	The Netherlands	Brain	Original Research	STXBP1-encephalopathy	Mice	Knockout mouse models	Abstract, Methods, Conclusion	21	In 1-3 sentences	Yes	No
Slaney (2018)	UK	Current Topics in Behavioral Neurosciences	Review	Depression	Not specified	Not specified	Body of Text	3	In 1-3 sentences	No	N/A
Flandreau (2018)	Hungary	Current Topics in Behavioral Neurosciences	Review	Post-traumatic stress disorder	Not specified	Not specified	Abstract, Body of Text	32	In 1-3 sentences	No	N/A
Wozinak (2018)	Poland	Pharmacology, Biochemistry and Behavior	Original Research	Schizophrenia	Mice	Chronic administration of MK-801	Abstract, Introduction, Methods, Conclusion	0	In 1-3 sentences	No	N/A
Yarborough (2018)	USA	PLOS Biology	Commentary	Neurological diseases and injuries	Not specified	Not specified	Introduction	9	Term only	No	N/A
Hart (2018)	The Netherlands	Clinical Pharmacology & Therapeutics	Review	Multiple Sclerosis	Not specified	Not specified	Body of Text, Conclusion	6	In 1-3 sentences	Yes	No
Mishra (2018)	India	Biochemical Pharmacology	Original Research	Parkinson's disease	Rats	6-hydroxydopamine model	Abstract, Introduction	4	In 1-3 sentences	No	N/A
Grimm (2018)	USA	Translational Psychiatry	Original Research	Schizophrenia	Mice	Cyclin-D2 knockout	Abstract, Discussion	4	In 1-3 sentences	No	N/A
Drozd (2018)	USA	Progress in Brain Research	Chapter	Autism spectrum disorders	Not specified	Not specified	Body of Text	0	10 or more sentences	Yes	Yes
Vendruscolo (2018)	USA	Neuropsychopharmacology	Original Research	Addiction	Rats	Sufentanil Vapor Self-Administration Model	Abstract, Conclusion	8	In 1-3 sentences	No	N/A
Badin (2018)	France	Methods in Molecular Biology, Huntington's Disease	Chapter	Huntington's Disease	Not specified	Not specified	Abstract, Body of Text	2	In 1-3 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
De La Pena (2018)	Republic of Korea	Molecular Neurobiology	Review	Attention-Deficient Hyperactivity Disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	9	10 or more sentences	Yes	No
Wolmarans (2018)	South Africa	Metabolic Brain Disease	Review	Obsessive-compulsive disorder	Deer mice	Not specified	Abstract, Body of Text	7	Term only	No	N/A
Ayuob (2018)	Saudi Arabia	Microscopy Research and Technique	Review	Depression	Not specified	Not specified	Abstract, Body of Text	1	In 1-3 sentences	Yes	No
Olaya (2018)	Australia	Schizophrenia Bulletin	Original Research	Schizophrenia	Mice	Transgenic model	Abstract, Body of Text	4	Term only	No	N/A
Robinson (2018)	UK	Philosophical Transactions	Review	Depression	Rodents	Not specified	Introduction, Body of Text	12	In 1-3 sentences	Yes	Yes
Saul (2018)	USA	PLoS One	Original Research	Mania	Mice	Genetic model	Abstract, Introduction, Discussion	0	In 1-3 sentences	No	N/A
Orengo (2018)	USA	Disease Models and Mechanisms	Original Research	Spinocerebellar ataxias	Mice	Knock-in model	Abstract, Introduction, Discussion	5	In 1-3 sentences	No	N/A
Mitra (2018)	USA	Behavioural Pharmacology	Original Research	Obsessive-compulsive disorder	Mice	Not specified	Introduction	7	In 1-3 sentences	No	N/A
Drapeau (2018)	USA	eNeuro	Original Research	Phelan–McDermid Syndrome	Mice	Knock-out model	Abstract, Introduction, Results, Discussion, Conclusion	5	In 1-3 sentences	No	N/A
Winter (2018)	Germany	Behavioural Brain Research	Original Research	Obsessive-compulsive disorder	Mice	Not specified	Abstract, Discussion, Conclusion	11	In 1-3 sentences	Yes	Yes
Pellerin (2018)	Canada	Platelets	Review	Fragile X Syndrome	Not specified	Knock-out model	Body of Text	6	Term only	No	N/A
Nicolini (2018)	Canada	Experimental Neurology	Review	Autism Spectrum Disorder	Mice	Drug induced model	Abstract, Introduction, Body of Text, Conclusion	91	4-10 sentences	Yes	No
Wolf (2018)	Germany	European Archives of Psychiatry and Clinical Neuroscience	Original Research	Schizophrenia	Rats	Not specified	Abstract, Discussion	1	In 1-3 sentences	No	N/A
Morrice (2018)	Canada	Neural Regeneration Research	Review	Amyotrophic lateral sclerosis	Not specified	Not specified	Abstract, Introduction, Body of Text, Conclusion	7	10 or more sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Rizzo (2018)	USA	Frontiers in Neurology	Original Research	Tourette syndrome and Attention deficit hyperactivity disorder	Rats	Striatal disinhibition paradigm	Abstract, Discussion, Conclusion	2	4-10 sentences	Yes	Yes
Paschoalin-Maurin (2018)	Brazil	Neuroscience	Original Research	Anxiety disorder and panic disorder	Rodents	Not specified	Abstract, Discussion, Conclusion	14	4-10 sentences	Yes	Yes
Wieschowski (2018)	Canada	PLOS Biology	Original Research	Not specified	Not specified	Not specified	Methods, Discussion	30	In 1-3 sentences	No	N/A
Kristensen (2018)	Denmark	Molecular Psychiatry	Systematic Review	Bipolar disorder	Mice	Genetic model	Introduction	5	Term only	Yes	No
Pappas (2018)	USA	The Journal of Clinical Investigation Insight	Original Research	Bipolar disorder	Mice	Genetic model	Abstract, Introduction, Discussion	16	4-10 sentences	No	N/A
Pittenger (2018)	USA	Histamine and Histamine Receptors in Health and Disease	Review	Tourette Syndrome	Mice	Knock-out model	Body of Text	15	In 1-3 sentences	No	N/A
Kristensen (2017)	Denmark	Molecular Psychiatry	Review	Bipolar disorder	Mice	Not specified	Introduction	5	In 1-3 sentences	No	N/A
Augustine (2017)	Canada	Stem Cells Translational Medicine	Systematic Review	Bronchopulmonary dysplasia	Not specified	Not specified	Methods	55	In 1-3 sentences	No	N/A
Spanagel (2017)	Germany	Dialogues in clinical neuroscience	Review	Addiction	Not specified	Not specified	Body of Text	42	In 1-3 sentences	Yes	Yes
Nielsen (2017)	Denmark	Translational Psychiatry	Original Research	Schizophrenia	Mice	Knock-out model	Abstract, Introduction	11	In 1-3 sentences	No	N/A
McGraw (2017)	USA	American Journal of Medical Genetics	Commentary	Neurobehavioral disorders	Rodents	Not specified	Abstract, Body of Text	3	4-10 sentences	Yes	No
Wang (2017)	USA	PLoS One	Original Research	Urologic chronic pelvic pain syndrome	Rats	Chronic water avoidance stress model	Abstract	9	Term only	No	N/A
Dekker (2017)	UK	Neurobiology of Disease	Original Research	Down syndrome	Mice	Ts65Dn model	Abstract, Introduction, Discussion, Conclusion	11	4-10 sentences	Yes	No
Farkas (2017)	Japan	Neuroscience	Original Research	Depression	Mice	Chronic variable mild stress	Abstract, Conclusion	15	In 1-3 sentences	Yes	Yes
Zeiss (2017)	USA	Institute for Laboratory Animal Research Journal	Review	Neurodegenerative Disease	Not specified	Not specified	Body of Text	3	Term only	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Kapadia (2017)	USA	Journal of Neuroimmune Pharmacology	Original Research	Systemic lupus erythematosus	Mice	Murphy Roths Large Mice Model	Abstract	4	Term only	No	N/A
Commons (2017)	USA	American Chemical Society: Chemical Neuroscience	Review	Depression	Rodents	Forced swim test	Abstract, Body of Text	126	4-10 sentences	Yes	No
Vinner (2017)	Israel	Journal of Neuroscience Methods	Original Research	Tic disorders	Rats	Not specified	Abstract, Discussion	7	In 1-3 sentences	Yes	No
Liu (2017)	China	Oncotarget	Original Research	Depression	Mice	Social isolation model	Abstract, Discussion	7	In 1-3 sentences	Yes	No
Shetty (2017)	India	Behavioural Brain Research	Original Research	Depression	Rats	Wistar-Kyoto	Abstract, Introduction	6	In 1-3 sentences	No	N/A
Vloo (2017)	Belgium	Pain	Review	Central poststroke pain	Not specified	Not specified	Abstract, Introduction, Discussion	13	4-10 sentences	Yes	Yes
Panaccione (2017)	Italy	Pharmacological Research	Original Research	Mania	Rats	Paradoxical sleep deprivation	Abstract, Introduction, Discussion	2	In 1-3 sentences	No	N/A
Bentea (2017)	Belgium	Journal of Parkinson's Disease	Review	Parkinson's Disease	Not specified	Proteasome Inhibition Model	Abstract, Body of Text	36	4-10 sentences	Yes	No
Wurbel (2017)	Switzerland	Lab Anim (NY)	Commentary	Not specified	Not specified	Not specified	Body of Text	21	In 1-3 sentences	Yes	N/A
Nasuti (2017)	Italy	Journal of Pharmacological and Toxicological Methods	Original Research	Parkinson's disease	Rats	Permethrin exposure model	Introduction, Discussion	21	In 1-3 sentences	Yes	Yes
Zike (2017)	USA	Neuroscience	Review	Obsessive-compulsive disorder	Rodents	Not specified	Abstract, Discussion, Body of Text	18	10 or more sentences	Yes	Yes
Van Kampen (2017)	Canada	EPMA Journal	Review	Parkinson's Disease	Rats	Beta-sitosterol beta-D-glucoside model	Abstract, Body of Text, Conclusion	6	In 1-3 sentences	Yes	No
Schlosser (2017)	Canada	Pulmonary Circulation	Review	Pulmonary arterial hypertension	Rodents	Not specified	Title, Abstract, Introduction	8	In 1-3 sentences	No	N/A
Kanyuch (2017)	USA	Schizophrenia Bulletin	Commentary	Schizophrenia	Not specified	Not specified	Body of Text	5	4-10 sentences	Yes	Yes
Philippens (2017)	The Netherlands	Drug Discovery Today: Disease Models	Review	Parkinson's Disease	Not specified	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model	Abstract, Body of Text	1	In 1-3 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Bahor (2016)	UK	Evidence-based Preclinical Medicine	Protocol	Psychosis	Not specified	Not specified	Introduction	1	In 1-3 sentences	No	N/A
Lauber (2016)	Switzerland	Frontiers in Molecular Medicine	Original research	Autism Spectrum Disorder	Mice	Drug induced model	Abstract, Introduction	25	In 1-3 sentences	No	N/A
Yael (2016)	Israel	Frontiers in Neuroscience	Review	Tourette syndrome	Not specified	Not specified	Abstract, Body of Text	8	4-10 sentences	Yes	Yes
Kostrzewa (2016)	USA	Current Topics in Behavioral Neurosciences	Review	Attention-Deficient Hyperactivity Disorder	Rodents	n6-OHDA-Lesioned Model	Body of Text	8	In 1-3 sentences	Yes	No
Mul (2016)	USA	eNeuro	Original Research	Depression	Mice	Forced swim test	Abstract, Introduction, Discussion	15	4-10 sentences	No	N/A
Gass (2016)	Germany	Translational Psychiatry	Original Research	Depression	Rats	Genetic model	Abstract, Introduction	12	In 1-3 sentences	No	N/A
Humby (2016)	UK	Psychoneuroendocrinology	Original Research	Postpartum psychosis	Mice	Pharmacological model	Abstract	12	In 1-3 sentences	Yes	Yes
Reber (2016)	USA	Psychoneuroendocrinology	Review	Post-traumatic stress disorder	Mice	Not specified	Abstract, Introduction, Body of Text	25	4-10 sentences	Yes	No
Suen (2016)	Canada	Systematic Reviews	Protocol	Pulmonary arterial hypertension	Not specified	Not specified	Methods	12	4-10 sentences	Yes	Yes
Avey (2016)	Canada	PLOS One	Systematic Review	Not specified	Not specified	Not specified	Introduction	40	In 1-3 sentences	No	N/A
Stoiljkovic (2016)	USA	Neurobiology of Aging	Original Research	Alzheimer's disease	Mice	Transgenic model	Abstract	6	Term only	No	N/A
Veeraragavan (2016)	USA	Human Molecular Genetics	Original Research	Rett syndrome	Rats	Methyl-CpG-Binding Protein 2	Discussion	29	In 1-3 sentences	Yes	Yes
Dirnagl (2016)	USA	Stroke	Report	Stroke	Rodents	Not specified	Body of Text	37	In 1-3 sentences	Yes	No
Swerdlow (2016)	USA	Current Topics Behavioral Neuroscience	Review	Schizophrenia	Not specified	Not specified	Abstract, Introduction, Conclusion	22	4-10 sentences	No	N/A
Mattina (2016)	Canada	Cancer Research	Systematic Review	Cancer	Rodents	Not specified	Abstract, Results, Discussion	14	4-10 sentences	Yes	No
Wolmarans (2016)	South Africa	Journal of Psychopharmacology	Original Research	Obsessive-compulsive disorder	Deer mice	Not specified	Introduction	14	In 1-3 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Butler (2016)	USA	Alcoholism: Clinical and Experimental Research	Review	Anxiety	Rats	Not specified	Abstract, Body of Text	57	4-10 sentences	Yes	No
Ren (2016)	Canada	Biological Psychiatric	Original Research	Depression	Mice	Transgenic model	Abstract, Introduction	51	In 1-3 sentences	No	N/A
Ryabinin (2016)	USA	International Review of Neurobiology	Chapter	Addicition	Prairie Voles	Not specified	Introduction, Body of Text	6	In 1-3 sentences	Yes	Yes
Pesarico (2016)	Brazil	Behavioural Brain Research	Original Research	Depression	Mice	Chronic unpredictable mild stress model	Abstract, Introduction	16	Term only	No	N/A
Lewis (2016)	USA	Critical Care Medicine	Original Research	Sepsis	Murine	Cecal Ligation and Puncture model	Abstract, Introduction, Methods, Results, Discussion, Conclusion	24	4-10 sentences	No	N/A
Perrine (2016)	USA	Behavioural Brain Research	Original Research	Post-traumatic stress disorder	Mice	Single prolonged stress model	Abstract, Introduction, Discussion	39	4-10 sentences	Yes	No
Becker (2016)	USA	Pharmacological Reviews	Review	Addicition	Not specified	Not specified	Abstract, Introduction, Body of Text	266	In 1-3 sentences	Yes	Yes
Hulbert (2016)	USA	Neuroscience	Review	Autism Spectrum Disorder	Mice	Not specified	Abstract, Body of Text	38	10 or more sentences	Yes	Yes
Ackerman (2016)	USA	American Journal of Physiology-Renal Physiology	Original Research	Visceral Pain Disorders	Rats	Stress-induced model	Abstract, Introduction, Body of Text	12	In 1-3 sentences	No	N/A
Burrows (2016)	Australia	Biological Psychology	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	18	10 or more sentences	Yes	Yes
Kostrzewa (2016)	USA	Neurochemical Research	Review	Schizophrenia	Rats	Ontogenetic quinpirole model	Abstract, Body of Text	10	In 1-3 sentences	Yes	No
Sharma (2016)	USA	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Mania	Rodents	Not specified	Abstract, Introduction, Body of Text	25	10 or more sentences	Yes	Yes
Cosgrove (2016)	USA	Biological Psychiatry	Commentary	Bipolar disorder	Rodents	Not specified	Introduction, Body of Text	38	4-10 sentences	Yes	No
Kimmelman (2016)	Canada	Journal of Medical Ethics	Review	Not specified	Not specified	Not specified	Body of Text	20	In 1-3 sentences	Yes	No
Logan (2016)	USA	Neuroscience	Review	Bipolar disorder	Not specified	Not specified	Abstract, Body of Text	58	10 or more sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Mo (2016)	Australia	Journal of Neuroscience Methods	Review	Huntington's Disease	Mice	Not specified	Abstract, Body of Text	22	4-10 sentences	Yes	Yes
Kato (2016)	Japan	Neuroscience	Review	Bipolar disorder	Not specified	Not specified	Abstract, Body of Text	22	4-10 sentences	Yes	Yes
Ko (2016)	Taiwan	Brain, Behavior, and Immunity	Original Research	Schizophrenia	Rats	Isolation rearing model	Abstract, Discussion	14	In 1-3 sentences	No	N/A
Godar (2016)	USA	British Journal of Pharmacology	Original Research	Tourette syndrome	Mice	D1CT-7	Abstract, Introduction, Discussion	21	4-10 sentences	Yes	No
Fifel (2016)	The Netherlands	Sleep Medicine Reviews	Review	Parkinson's Disease	Not specified	Not specified	Abstract, Body of Text	18	4-10 sentences	Yes	No
Foote (2016)	USA	Cerebellum	Review	Fragile X-associated tremor/ataxia syndromeFragile-X	Mice	Not specified	Abstract, Body of Text	5	4-10 sentences	Yes	Yes
Lalu (2016)	Canada	eLife	Systematic Review	Sepsis	Not specified	Not specified	Introduction, Methods, Results, Discussion	35	10 or more sentences	Yes	Yes
Bruin (2015)	Germany	Current Pharmaceutical Design	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	79	Term only	No	N/A
Alonso (2015)	Spain	Neuropsychiatric Disease and Treatment	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text	45	10 or more sentences	Yes	Yes
Ruhela (2015)	India	Annals of Neurosciences	Review	Autism Spectrum Disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	16	4-10 sentences	Yes	Yes
Bentea (2015)	USA	Frontiers in Behavioral Science	Original Research	Parkinson's disease	Mice	Proteasome inhibition model	Abstract, Discussion, Conclusion	29	In 1-3 sentences	No	N/A
Henderson (2015)	Canada	eLife	Systematic Review	Cancer	Rats & mice	Not specified	Methods, Results. Discussion	29	4-10 sentences	Yes	Yes
Cenci (2015)	Sweden	Neurobiology of Disease	Review	Parkinson's disease	Rodents	Not specified	Methods, Results. Discussion	13	In 1-3 sentences	No	N/A
Brunner (2015)	USA	PLOS One	Original Research	Autism Spectrum Disorder	Mice	16p11.2 Deletion and Null Cntnap2 mouse models	Abstract, Introduction, Discussion	36	4-10 sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Servadio (2015)	Italy	Animal models in autism research	Review	Autism Spectrum Disorder	Rodents	Not specified	Abstract, Introduction, Body of Text	34	4-10 sentences	Yes	N/A
Wang (2015)	USA	International Journal of Neuropsychopharmacology	Original Research	Schizophrenia	Mice	Methionine-Induced	Discussion, Conclusion	13	In 1-3 sentences	No	N/A
Wallace (2015)	USA	Handbook of Experimental Pharmacology	Chapter	Cognitive impairments	Not specified	Not specified	Abstract, Body of Text, Conclusion	13	4-10 sentences	No	N/A
Streck (2015)	Brazil	Neurochemical Research	Original Research	Sleep disorders	Mice	Drug induced model	Abstract, Conclusion	9	In 1-3 sentences	No	N/A
Mokoena (2015)	South Africa	Psychopharmacology	Original Research	Depression	Rats	Flinders Sensitive Line	Abstract, Discussion	33	In 1-3 sentences	Yes	No
Grone (2015)	USA	Nature Neuroscience	Commentary	Epilepsy	Not specified	Not specified	Introduction	83	In 1-3 sentences	Yes	No
Varga (2015)	Hungary	Obesity reviews	Review	Diabetes	Not specified	Not specified	Discussion	3	In 1-3 sentences	Yes	Yes
Xu (2015)	China	Scientific reports	Original Research	Depression	Macaques	Naturally occurring	Introduction, Discussion	19	4-10 sentences	Yes	No
Leao (2015)	Brazil	Brain Pathology	Review	Parkinson's Disease	Not specified	Not specified	Abstract, Body of Text	51	In 1-3 sentences	No	N/A
Perren (2015)	Belgium	Neurobiology of Aging	Original Research	Parkinson's Disease	Rats	Viral vector-based	Discussion	58	In 1-3 sentences	Yes	No
O'Connor (2015)	Ireland	Pharmacology & Therapeutics	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	21	4-10 sentences	Yes	No
Bernard (2015)	USA	Experimental Neurology	Commentary	Seizures	Rodents	Not specified	Abstract, Body of Text	19	In 1-3 sentences	Yes	No
Mo (2015)	Australia	Behavioural Brain Research	Original Research	Huntington's Disease	Mice	Transgenic model	Abstract, Introduction	9	Term only	No	N/A
Stewart (2015)	USA	Behavioural Brain Research	Review	Brain Disorders	Not specified	Not specified	Abstract, Body of Text	83	In 1-3 sentences	Yes	Yes
Tyurenkov (2015)	Russia	Neuroscience and Behavioral Physiology	Original Research	Depression	Rats	Chronic combined stress	Abstract, Discussion, Conclusion	2	4-10 sentences	Yes	Yes
Zurawek (2015)	USA	Dopamine Receptor Technologies	Chapter	Depression	Rats	Not specified	Abstract	5	Term only	No	N/A
Hirst (2014)	UK	Evidence-based Preclinical Medicine	Systematic Review	Cerebral glioma	Rats & mice	Not specified	Discussion, Conclusion		In 1-3 sentences	Yes	No
Garner (2014)	USA	Journal of the Institute for Laboratory Animal Research	Review	Not specified	Not specified	Not specified	Body of Text	82	4-10 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Bey (2014)	USA	Current Protocols in Pharmacology	Review	Autism Spectrum Disorder	Mice	Not specified	Abstract, Introduction, Body of Text, Conclusion	32	10 or more sentences	Yes	No
Lalu (2014)	Canada	Systematic Reviews	Protocol	Acute Lung Injury	Not specified	Not specified	Methods	32	4-10 sentences	Yes	No
Mead (2014)	USA	Expert Opinion on Drug Discovery	Commentary	Addicition	Not specified	Not specified	Body of Text	11	In 1-3 sentences	No	N/A
Hagihara (2014)	Japan	Molecular Brain	Original Research	Schizophrenia	Mice	Knock-out model	Abstract, Results	34	In 1-3 sentences	No	N/A
McOmish (2014)	Australia	British Journal of Pharmacology	Review	Psychiatric Disorders	Not specified	Not specified	Abstract, Body of Text, Conclusion	27	10 or more sentences	Yes	No
Theilmann (2014)	Germany	Journal of Psychiatric Research	Original Research	Depression	Rats	Electroconvulsive stimulation models	Title, Abstract, Introduction, Discussion, Conclusion	6	4-10 sentences	No	N/A
Weerasinghe (2014)	UK	European Journal of Pain	Original Research	Chronic Pain	Rats	UVB and heat rekindling model	Abstract, Introduction, Discussion	6	4-10 sentences	Yes	No
Bilkei-Gorzo (2014)	Germany	Pharmacology & Therapeutics	Review	Alzheimer's Disease	Mice	Not specified	Abstract, Introduction, Body of Text, Conclusion	136	4-10 sentences	Yes	No
Mergy (2014)	USA	Neurochemistry International	Review	Attention-Deficient Hyperactivity Disorder	Mice	Not specified	Abstract, Discussion	26	In 1-3 sentences	No	N/A
Brown (2014)	USA	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Original Research	Schizophrenia	Mice	Drug induced model	Introduction, Discussion, Conclusion	35	In 1-3 sentences	No	N/A
Pittman (2014)	USA	Physiology & Behavior	Original Research	Depression & Anxiety	Zebrafish	Not specified	Abstract, Introduction, Conclusion	38	In 1-3 sentences	Yes	No
Kas (2014)	The Netherlands	Psychopharmacology	Review	Autism Spectrum Disorder	Rodents	Not specified	Abstract, Discussion, Body of Text	69	4-10 sentences	Yes	No
McGonigle (2014)	USA	Biochemical Pharmacology	Review	Not specified	Not specified	Not specified	Body of Text	316	In 1-3 sentences	Yes	Yes
McGonigle (2014)	USA	Biochemical Pharmacology	Review	Not specified	Not specified	Not specified	Body of Text	101	In 1-3 sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Rezin (2014)	Brazil	Molecular Neurobiology	Original Research	Bipolar disorder	Rats	Drug induced model	Abstract, Introduction, Methods	27	4-10 sentences	Yes	No
Jithendra (2014)	India	Journal of Chemical and Pharmaceutical Sciences	Original Research	Obsessive-compulsive disorder	Rats	Drug induced model	Abstract, Discussion, Conclusion	0	In 1-3 sentences	No	N/A
Ngoupaye (2013)	South Africa	BMC Complementary and Alternative Medicine	Original Research	Epilepsy	Rats	Forced swim test	Abstract, Discussion	19	In 1-3 sentences	No	N/A
Abelaira (2013)	Brazil	Revista Brasileira de Psiquiatria	Review	Depression	Not specified	Not specified	Abstract, Introduction, Body of Text, Conclusion	159	4-10 sentences	Yes	No
Gobira (2013)	Brazil	Revista Brasileira de Psiquiatria	Review	Schizophrenia	Not specified	Not specified	Abstract, Introduction, Body of Text, Conclusion	33	4-10 sentences	Yes	Yes
Du (2013)	Australia	Frontiers in Neurology	Review	Huntington's Disease	Not specified	Not specified	Abstract	29	Term only	No	N/A
Miczek (2013)	USA	Psychopharmacology	Review	Agression	Not specified	Not specified	Abstract, Body of Text	57	4-10 sentences	Yes	No
Moore (2013)	USA	Neuroscience and Biobehavioral Reviews	Editorial	Schizophrenia	Not specified	Not specified	Abstract, Introduction, Body of Text, Conclusion	42	10 or more sentences	No	N/A
Lauijssens (2013)	France	Translational pharmacology	Review	Alzheimer's Disease	Not specified	Not specified	Abstract, Body of Text	76	4-10 sentences	Yes	Yes
Wolmarans (2013)	South Africa	Behavioural Brain Research	Original Research	Obsessive-compulsive disorder	Deer mice	Not specified	Abstract, Introduction, Discussion, Conclusion	25	4-10 sentences	Yes	Yes
Micale (2013)	Czech Republic	Cell and Tissue Research	Review	Depression & schizophrenia	Rodents	Not specified	Introduction, Body of Text	44	In 1-3 sentences	Yes	No
Henderson (2013)	Canada	PLOS Medicine	Systematic review	Not specified	Not specified	Not specified	Abstract, Introduction, Methods, Results, Discussion	213	10 or more sentences	Yes	No
Siegel (2013)	USA	Neuroscience and Biobehavioral Reviews	Review	Schizophrenia	Rodents	Not specified	Abstract, Body of Text	29	4-10 sentences	No	N/A
Vollmayr (2013)	Germany	Cell and Tissue Research	Review	Depression	Not specified	Not specified	Abstract, Body of Text, Conclusion	64	4-10 sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Moreira (2013)	Brazil	Cell Tissue Research	Review	Panic disorders	Rodents	Not specified	Abstract, Introduction, Body of Text, Conclusion	49	4-10 sentences	Yes	No
Burrows (2013)	Australia	CNS & Neurological Disorders - Drug Targets	Review	Central nervous system disorders	Not specified	Not specified	Title, Abstract, Body of Text, Conclusion	13	10 or more sentences	Yes	No
Zemanova (2013)	Czech Republic	Pharmacology, Biochemistry and Behavior	Original Research	Schizophrenia	Rats	Acute MK-801 induction	Introduction	21	In 1-3 sentences	Yes	No
Kelley (2013)	USA	Brain, Behavior, and Immunity	Original Resarch	Depression	Mice	Inflammation induced	Abstract, Discussion	40	In 1-3 sentences	No	N/A
Roullet (2013)	Canada	Neurotoxicology and Teratology	Review	Autism Spectrum Disorder	Rodents	Drug induced model	Abstract, Conclusion	257	In 1-3 sentences	No	N/A
Marquez (2013)	Switzerland	Translational Psychiatry	Original Research	Pathological aggression	Rats	Peripubertal stress exposure model	Abstract, Discussion, Conclusion	186	In 1-3 sentences	Yes	No
Mulcahy (2013)	Ireland	Behavioural Brain Research	Original Research	Parkinson's Disease	Rats	Gene-transfer model	Abstract, Introduction, Conclusion	26	In 1-3 sentences	No	N/A
El-Kordi (2013)	Germany	Behavioural Brain Research	Original Research	Autism Spectrum Disorder	Mice	Nlgn4 null mutant model	Title, Abstract, Introduction, Conclusion	78	In 1-3 sentences	No	N/A
Vervliet (2013)	Belgium	Psychological Medicine	Editorial	Anxiety & depression	Not specified	Not specified	Abstract, Body of Text, Conclusion	70	10 or more sentences	Yes	Yes
Lipina (2013)	Canada	Neuropsychopharmacology	Original Research	Depression	Mice	Genetic model	Abstract, Introduction, Discussion	37	In 1-3 sentences	Yes	Yes
Homberg (2013)	The Netherlands	Behavioural Brain Research	Review	Neuropsychiatric disorders	Not specified	Not specified	Body of Text, Conclusion	49	10 or more sentences	Yes	No
Ciccocioppo (2013)	Italy	Current Topics in Behavioral Neurosciences	Review	Alcoholism	Rats	Genetic model	Abstract, Body of Text	30	4-10 sentences	Yes	Yes
Cifani (2013)	Italy	Animal Models of Eating Disorders	Original Research	Binge eating disorder	Rats	Highly palatable food model	Abstract, Conclusion	6	In 1-3 sentences	No	N/A
Johnson (2012)	USA	Physiology & Behavior	Review	Panic disorders	Not specified	Not specified	Abstract, Body of Text, Conclusion	42	4-10 sentences	No	N/A
Peleg-Raibstein (2012)	Switzerland	Current Antipsychotics	Chapter	Schizophrenia	Not specified	Not specified	Body of Text	29	4-10 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Young (2012)	USA	Novel Antischizophrenia Treatments	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	17	4-10 sentences	No	N/A
Hamani (2012)	The Netherlands	Science Translational Medicine	Review	Psychiatric disorders	Not specified	Not specified	Body of Text	102	In 1-3 sentences	No	N/A
Foley (2012)	Ireland	Neuropharmacology	Original Research	Autism Spectrum Disorder	Rats	Drug induced model	Abstract, Introduction, Discussion	55	4-10 sentences	No	N/A
Iderberg (2012)	Sweden	Neuroscience	Review	Parkinson's disease	Not specified	Not specified	Conclusion	59	In 1-3 sentences	Yes	No
Flood (2012)	USA	Neuroscience	Original Research	Autism Spectrum Disorder	Mice	Not specified	Abstract, Introduction, Discussion, Conclusion	12	4-10 sentences	No	N/A
Taneja (2012)	The Netherlands	Drug Discovery Today	Review	Neuropathic pain	Not specified	Not specified	Abstract, Discussion, Body of Text, Conclusion	33	4-10 sentences	Yes	No
Modi (2012)	USA	Hormones and Behavior	Review	Autism Spectrum Disorder	Not specified	Not specified	Abstract, Introduction, Body of Text	182	4-10 sentences	Yes	No
Brunner (2012)	USA	Behavioural Processes	Review	Central nervous system disorders	Not specified	Not specified	Abstract, Body of Text	23	4-10 sentences	No	N/A
Yanagi (2012)	USA	Progress in Molecular Biology and Translational Science	Chapter	Schizophrenia	Not specified	Not specified	Title, Abstract, Introduction, Body of Text, Conclusion	13	10 or more sentences	Yes	Yes
Adell (2012)	Spain	Schizophrenia Bulletin	Review	Schizophrenia	Rodents	Acute NMDA Receptor Hypofunction model	Abstract, Body of Text	108	In 1-3 sentences	No	N/A
Albelda (2012)	Israel	Neuroscience	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	75	10 or more sentences	Yes	Yes
Harrison (2012)	UK	Neuropharmacology	Commentary	Schizophrenia	Mice	Genetic model	Abstract, Body of Text	20	In 1-3 sentences	No	N/A
Young (2012)	USA	Neuropharmacology	Review	Schizophrenia	Mice	Not specified	Introduction, Discussion	34	In 1-3 sentences	No	N/A
Albelda (2012)	Israel	Neuroscience and Biobehavioral Reviews	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	122	10 or more sentences	Yes	Yes
Koob (2012)	Germany	Handbook of Clinical Neurology	Chapter	Psychiatric disorders	Not specified	Not specified	Body of Text, Conclusion	32	10 or more sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Parle (2012)	India	International Research Journal of Pharmacy	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text, Conclusion	3	10 or more sentences	Yes	No
Chatterjee (2012)	India	Neuropharmacology	Original Research	Schizophrenia	Mice	Ketamine induced model	Introduction, Discussion	95	In 1-3 sentences	No	N/A
Sartori (2011)	Austria	Future Neurology	Review	Anxiety	Mice	Not specified	Abstract, Body of Text	50	4-10 sentences	Yes	No
Honore (2011)	Denmark	Scandinavian Journal of Pain	Review	Neuropathic pain	Not specified	Not specified	Introduction	6	In 1-3 sentences	Yes	No
Freitas (2011)	Brazil	Acta Neuropsychiatrica	Original Research	Bipolar disorder	Rats	Ketamine induced model	Abstract, Introduction, Conclusion	3	4-10 sentences	Yes	No
Belzung (2011)	France	Biology of Mood & Anxiety Disorders	Review	Anxiety & depression	Not specified	Not specified	Abstract, Body of Text	226	10 or more sentences	Yes	Yes
Trivedi (2011)	USA	Indian Journal of Pharmacology	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	6	4-10 sentences	Yes	No
Takahashi (2011)	USA	Translational Psychiatry	Original Research	Schizophrenia	Mice	Transgenic model	Abstract, Body of Text	29	In 1-3 sentences	No	N/A
Kluge (2011)	UK	Expert Review of Molecular Diagnostics	Review	Schizophrenia & depression	Not specified	Not specified	Abstract, Introduction, Body of Text	19	4-10 sentences	Yes	Yes
Fineberg (2011)	UK	British Journal of Pharmacology	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text	55	4-10 sentences	Yes	Yes
Modi (2011)	USA	Biological Psychiatry	Original Research	Autism Spectrum Disorder	Prairie and meadow voles	Drug induced model	Abstract, Discussion, Conclusion	42	4-10 sentences	No	N/A
Winstanley (2011)	Canada	British Journal of Pharmacology	Review	Impulse control disorders	Rats	Not specified	Body of Text	184	In 1-3 sentences	No	N/A
Young (2011)	USA	British Journal of Pharmacology	Review	Mania	Not specified	Not specified	Body of Text	101	In 1-3 sentences	No	N/A
Pietropaolo (2011)	Italy	PLoS One	Original Research	Autism Spectrum Disorder	Mice	Knock-out model	Abstract, Introduction	117	In 1-3 sentences	No	N/A
Zoratto (2011)	Italy	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Depression	Not specified	Not specified	Abstract, Body of Text, Conclusion	15	4-10 sentences	Yes	No
Greene (2011)	USA	Behavioural Brain Research	Original Research	Obsessive-compulsive disorder	Mice	Marble burying non-induced model	Introduction, Discussion	60	In 1-3 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Luyten (2011)	Belgium	Cognitive, Affective, & Behavioral Neuroscience	Review	Anxiety	Rats	Not specified	Abstract, Introduction, Body of Text, Conclusion	48	10 or more sentences	Yes	Yes
Patterson (2011)	USA	Pediatric Research	Review	Autism Spectrum Disorder	Rats & mice	Not specified	Abstract, Body of Text	123	In 1-3 sentences	Yes	No
Bari (2011)	UK	Molecular and Functional Models in Neuropsychiatry	Chapter	Attention-Deficient Hyperactivity Disorder	Not specified	Not specified	Body of Text	16	4-10 sentences	Yes	Yes
Vickers (2011)	UK	British Journal of Pharmacology	Review	Obesity	Not specified	Not specified	Body of Text	84	4-10 sentences	Yes	No
O'Connor (2011)	Ireland	Pharmacology & Therapeutics	Review	Traumatic brain injury	Not specified	Not specified	Abstract, Body of Text	162	4-10 sentences	Yes	No
Paterson (2011)	USA	Biochemical Pharmacology	Review	Substance use disorders	Not specified	Not specified	Body of Text	12	In 1-3 sentences	No	N/A
Stone (2011)	USA	Current Protocols in Neuroscience	Commentary	Depression	Mice	Open-space forced swim model	Abstract, Body of Text	23	In 1-3 sentences	No	N/A
Burrows (2011)	Australia	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Psychiatric disorders	Rats & mice	Not specified	Title, Abstract, Introduction, Body of Text	54	10 or more sentences	Yes	No
Yang (2011)	USA	Neurobiology of Huntington's Disease: Applications to Drug Discovery.	Chapter	Huntington's Disease	Mice	Not specified	Body of Text	15	4-10 sentences	Yes	Yes
Neumann (2011)	Sweden	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Depression	Rats & mice	Not specified	Abstract, Introduction, Body of Text	147	4-10 sentences	Yes	No
Bouet (2011)	France	Neuroscience Letters	Report	Schizophrenia	Mice	Separation & social isolation model	Abstract, Body of Text	20	In 1-3 sentences	No	N/A
Sarkisova (2011)	Russia	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Epilepsy and depression	Rats	Genetic model	Body of Text, Conclusion	141	In 1-3 sentences	No	N/A
Pryce (2011)	Switzerland	Psychoneuroendocrinology	Review	Depression	Mice	Not specified	Abstract, Body of Text, Conclusion	46	10 or more sentences	Yes	No
Scheggi (2011)	Italy	International Journal of	Original Research	Anhedonia	Rats	Cocaine sensitization model	Abstract, Discussion	17	In 1-3 sentences	Yes	No

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
		Neuropsychopharmacology									
Wadenberg (2010)	Sweden	Current Pharmaceutical Design	Review	Schizophrenia	Not specified	Not specified	Body of Text	66	4-10 sentences	Yes	Yes
Varga (2010)	Portugal	Alternatives to Laboratory Animals	Commentary	Not specified	Not specified	Not specified	Body of Text	49	In 1-3 sentences	Yes	Yes
Chimakurthy (2010)	India	North American Journal of Medical Sciences	Original Research	Obsessive-compulsive disorder	Rats	Drug induced model	Title, Abstract, Discussion, Conclusion	7	In 1-3 sentences	No	N/A
Sontag (2010)	Germany	ADHD Attention Deficit and Hyperactivity Disorders	Review	Attention-Deficient Hyperactivity Disorder	Not specified	Not specified	Abstract, Discussion, Body of Text	61	10 or more sentences	Yes	Yes
Treit (2010)	Canada	Current Topics in Behavioral Neurosciences	Review	Anxiety	Not specified	Not specified	Abstract, Body of Text	46	4-10 sentences	Yes	Yes
Jucker (2010)	Germany	Nature Research	Commentary	Neurodegenerative diseases	Not specified	Not specified	Not mentioned	275	N/A	No	N/A
Shelley (2010)	Canada	Studies in History and Philosophy of Biological and Biomedical Sciences	Review	Not specified	Not specified	Not specified	Body of Text	16	10 or more sentences	Yes	Yes
Wilson (2010)	USA	Clinical Schizophrenia & Related Psychoses	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	50	4-10 sentences	Yes	No
Takumi (2010)	Japan	Brain & Development	Review	Autism Spectrum Disorder	Mice	Genetic model	Abstract, Body of Text	15	In 1-3 sentences	Yes	Yes
Klein (2010)	Switzerland	Psychopharmacology	Original Research	Panic disorders	Rats	Ultrasound-induced wild running	Abstract, Introduction, Discussion, Body of Text	19	4-10 sentences	Yes	No
Maximino (2010)	Brazil	Behavioural Brain Research	Review	Anxiety	Zebrafish	Not specified	Abstract, Body of Text	334	10 or more sentences	Yes	Yes
Duman (2010)	USA	Vitamins and Hormones	Chapter	Depression	Not specified	Not specified	Abstract, Body of Text	152	4-10 sentences	Yes	Yes
Radyushkin (2010)	Germany	Genes, Brain and Behavior	Original Research	Schizophrenia	Mice	Genetic-environmental model	Abstract, Introduction, Discussion	31	In 1-3 sentences	Yes	Yes
Maximino (2010)	Brazil	Psychology & Neuroscience	Review	Anxiety	Not specified	Not specified	Title, Abstract, Introduction, Body of Text, Conclusion	14	4-10 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Vucetic (2010)	USA	Neuroscience	Original Research	Neurobehavioral disorders	Mice	Not specified	Abstract, Conclusion	107	In 1-3 sentences	No	N/A
Inagaki (2010)	Japan	Pharmacology, Biochemistry and Behavior	Original Research	Anxiety	Rats	Pheromone-induced	Introduction, Conclusion	19	In 1-3 sentences	Yes	Yes
Jornada (2010)	Brazil	Journal of Psychiatric Research	Original Research	Bipolar disorder	Rats	Drug induced model	Abstract, Introduction, Conclusion	67	In 1-3 sentences	Yes	Yes
Feleder (2010)	USA	Biological Psychiatry	Original Research	Schizophrenia	Rats	Neonatal ventral hippocampal lesion model	Abstract, Introduction	63	In 1-3 sentences	No	N/A
Meyer (2010)	Switzerland	Progress in Neurobiology	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	346	10 or more sentences	Yes	Yes
Young (2010)	USA	Behavioral Neurobiology of Schizophrenia and Its Treatment	Review	Schizophrenia	Not specified	Not specified	Abstract, Body of Text	98	10 or more sentences	Yes	Yes
van der Staay (2009)	The Netherlands	Behavioral and Brain Functions	Review	Neurobehavioral disorders	Not specified	Not specified	Abstract, Introduction, Body of Text	216	10 or more sentences	Yes	Yes
Mayer (2009)	USA	Digestive Disease	Review	Functional gastrointestinal disorders	Not specified	Not specified	Abstract, Body of Text	12	In 1-3 sentences	No	N/A
Lu (2009)	USA	International Review of Neurobiology	Chapter	Neurodegenerative disorders	Not specified	Not specified	Abstract, Body of Text	5	10 or more sentences	Yes	Yes
Boulougouris (2009)	UK	Psychiatry Research	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text	47	4-10 sentences	Yes	Yes
Castagné (2009)	France	Advances in Pharmacology	Chapter	Schizophrenia	Not specified	Not specified	Introduction	63	In 1-3 sentences	Yes	Yes
Hendrie (2009)	UK	Medical Hypotheses	Review	Depression	Not specified	Not specified	Body of Text	32	In 1-3 sentences	No	N/A
Nagakura (2009)	Japan	Pain	Original Research	Fibromyalgia	Rats	Not specified	Abstract, Discussion, Conclusion	138	In 1-3 sentences	No	N/A
Razzoli (2009)	Italy	Psychoneuroendocrinology	Original Research	Social stress	Rats	Social defeat model	Abstract, Introduction, Conclusion	36	In 1-3 sentences	No	N/A
Takeda (2009)	Japan	Brain Research	Original Research	Alzheimer's Disease	Mice	β-amyloid peptide model	Abstract, Introduction, Discussion	58	4-10 sentences	Yes	No
Ashkenazy (2009)	Israel	Behavioural Brain Research	Report	Depression & anxiety	Rodents	Not specified	Abstract, Body of Text	65	In 1-3 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Malkesman (2009)	USA	Disease Models & Mechanisms	Review	Bipolar disorder	Not specified	Not specified	Abstract, Body of Text	57	10 or more sentences	Yes	Yes
Peleg-Raibstein (2009)	Switzerland	Psychopharmacology	Original Research	Schizophrenia	Rats	Amphetamine sensitization model	Abstract, Introduction, Discussion, Conclusion	29	In 1-3 sentences	No	N/A
Elmer (2009)	USA	Schizophrenia Bulletin	Report	Psychiatric Illness	Not specified	Not specified	Abstract, Body of Text	8	4-10 sentences	No	N/A
Morsink (2009)	The Netherlands	Advances in Physiology Education	Report	Psychiatric or neurological disease	Not specified	Not specified	Abstract, Introduction, Methods, Results, Discussion	6	10 or more sentences	Yes	No
O'Dell (2009)	USA	Pharmacology, Biochemistry and Behavior	Review	Nicotine addiction	Rodents	Not specified	Abstract, Introduction, Body of Text	73	4-10 sentences	Yes	Yes
Markou (2009)	USA	Neuropsychopharmacology	Review	Central nervous system disorders	Not specified	Not specified	Abstract, Body of Text	317	10 or more sentences	Yes	Yes
Malatynska (2008)	USA	Mood and Anxiety Related Phenotypes in Mice	Chapter	Depression	Rats & mice	Not specified	Body of Text	1	In 1-3 sentences	No	N/A
Sagvolden (2008)	USA	Behavioral and Brain Functions	Original Research	Attention-Deficient Hyperactivity Disorder	Rats	Spontaneously model	Abstract, Introduction	63	In 1-3 sentences	Yes	Yes
Schmidt (2008)	Germany	Annals of the New York Academy of Sciences	Review	Chronic stress associated diseases	Not specified	Not specified	Abstract, Body of Text	77	4-10 sentences	Yes	Yes
Gerlach (2008)	Germany	Parkinsonism and Related Disorders	Review	Parkinson's Disease	Not specified	Neuromelanin-bound ferric iron	Abstract, Conclusion	29	In 1-3 sentences	Yes	No
Miczek (2008)	USA	Psychopharmacology	Review	Psychiatric disorders	Not specified	Not specified	Abstract, Body of Text	26	4-10 sentences	No	N/A
McNaughton (2008)	New Zealand	Handbook of Behavioral Neuroscience	Chapter	Anxiety	Not specified	Not specified	Abstract, Body of Text	44	10 or more sentences	Yes	Yes
Kasahara (2008)	Japan	PLoS One	Original Research	Bipolar disorder	Mice	Transgenic model	Introduction	10	In 1-3 sentences	Yes	No
Pratt (2008)	UK	British Journal of Pharmacology	Review	Schizophrenia	Rats	N-methyl-D-aspartate receptor antagonist	Introduction, Body of Text	138	In 1-3 sentences	No	N/A
Benedetti (2008)	Italy	Behavioural Brain Research	Original Research	Mania	Mice	Sleep deprivation model	Abstract, Introduction, Discussion	65	In 1-3 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Korff (2008)	South Africa	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Original Research	Obsessive-compulsive disorder	Deer mice	Drug induced model	Introduction	83	In 1-3 sentences	No	N/A
Risbrough (2008)	USA	Oxford Handbook of Anxiety and Related Disorders	Chapter	Anxiety	Not specified	Not specified	Introduction, Body of Text	4	4-10 sentences	Yes	Yes
McOmish (2008)	Australia	Molecular Psychiatry	Original Research	Schizophrenia	Mice	Knock-out model	Discussion	133	In 1-3 sentences	No	N/A
Crawley (2007)	USA	Brain Pathology	Review	Autism Spectrum Disorder	Mice	Not specified	Abstract, Body of Text	506	In 1-3 sentences	No	N/A
Herman (2007)	USA	Neuroscience and Biobehavioral Reviews	Review	Bipolar disorder	Rats	Ouabain induced model	Abstract, Introduction	56	In 1-3 sentences	Yes	No
Maccari (2007)	France	Psychoneuroendocrinology	Review	Not specified	Rats	Prenatal restraint stress model	Body of Text	314	In 1-3 sentences	Yes	Yes
Kato (2007)	Japan	Neuroscience and Biobehavioral Reviews	Review	Bipolar Disorder	Not specified	Not specified	Abstract, Body of Text	84	4-10 sentences	Yes	Yes
Berretta (2006)	USA	Nature Protocols	Original Research	Schizophrenia	Rats	Isomorphic model	Abstract, Introduction	13	In 1-3 sentences	No	N/A
Sarter (2006)	USA	Trends in Pharmacological Sciences	Review	Neuropsychiatric and neurological disorders	Not specified	Not specified	Body of Text	43	4-10 sentences	Yes	Yes
McArthur (2006)	Italy	Pharmacology, Biochemistry and Behavior	Review	Depression	Not specified	Not specified	Body of Text	220	4-10 sentences	Yes	Yes
Day-Wilson (2006)	UK	Neuroscience	Original Research	Schizophrenia	Rats	Isolation rearing model	Abstract, Introduction, Discussion, Conclusion	118	4-10 sentences	No	N/A
Swerdlow (2006)	USA	Tourette Syndrome	Review	Tourette Syndrome	Not specified	Not specified	Body of Text, Conclusion	44	10 or more sentences	Yes	Yes
Leveleki (2006)	Hungary	Brain Research Bulletin	Original Research	Anxiety	Rats	Stress-induced social avoidance model	Abstract, Discussion, Conclusion	34	In 1-3 sentences	No	N/A
Van der Staay (2006)	The Netherlands	Brain Research Reviews	Review	Behavioural disorders	Not specified	Not specified	Abstract, Body of Text	212	10 or more sentences	Yes	Yes
Frey (2006)	Brazil	Life Sciences	Original Research	Bipolar disorder	Rats	D-amphetamine induced model	Abstract, Introduction	68	In 1-3 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Joel (2006)	Israel	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Obsessive-compulsive disorder	Not specified	Not specified	Abstract, Body of Text	177	10 or more sentences	Yes	Yes
Ohl (2005)	The Netherlands	Anxiety and Anxiolytic Drugs	Chapter	Anxiety	Not specified	Not specified	Body of Text	78	In 1-3 sentences	No	N/A
Winston (2005)	USA	Pain	Original Research	Chronic pancreatitis	Rats	Trinitrobenzene sulfonic acid induced model	Abstract, Discussion	89	In 1-3 sentences	Yes	Yes
Swerdlow (2005)	USA	Pharmacology & Therapeutics	Review	Tourette Syndrome	Not specified	Not specified	Abstract, Body of Text	63	10 or more sentences	Yes	Yes
Sagvolden (2005)	South Africa	Biological Psychiatry	Review	Attention-Deficient Hyperactivity Disorder	Rodents	Not specified	Abstract, Body of Text, Conclusion	466	4-10 sentences	Yes	Yes
Pryce (2005)	Switzerland	Neuroscience and Biobehavioral Reviews	Review	Depression	Rodents and Primates	Not specified	Abstract, Introduction, Conclusion	409	4-10 sentences	No	N/A
Anisman (2005)	Canada	Neuroscience and Biobehavioral Reviews	Review	Depression	Not specified	Not specified	Abstract, Body of Text, Conclusion	556	In 1-3 sentences	Yes	Yes
Barr (2005)	USA	Neuroscience and Biobehavioral Reviews	Review	Depression	Not specified	Psychostimulant withdrawal model	Abstract, Introduction, Conclusion	116	4-10 sentences	Yes	Yes
Lubow (2005)	Israel	Schizophrenia Bulletin	Review	Schizophrenia	Not specified	Attentional Model	Title, Introduction, Body, Conclusion	202	10 or more sentences	Yes	Yes
Fuchs (2005)	Germany	CNS Spectrums	Review	Depression	Shrews	Not specified	Introduction	156	In 1-3 sentences	Yes	Yes
Crawley (2004)	USA	Mental Retardation and Developmental Disabilities Research Reviews	Review	Autism Spectrum Disorder	Mice	Not specified	Abstract	399	In 1-3 sentences	Yes	No
Kalueff (2004)	Finland	Acta Neurobiologiae Experimentalis	Review	Anxiety & Depression	Not specified	Not specified	Body of Text	169	4-10 sentences	Yes	No
Ruedi-Bettschen (2004)	Switzerland	Behavioural Pharmacology	Original Research	Depression	Rats	Early deprivation model	Discussion	27	In 1-3 sentences	No	N/A
Corwin (2004)	USA	Physiology & Behavior	Review	Binge eating	Not specified	Not specified	Abstract, Body of Text	188	4-10 sentences	Yes	Yes
Fiefel (2003)	USA	Neuropsychopharmacology	Original Research	Schizophrenia	Rats	Genetic model	Conclusion	72	In 1-3 sentences	No	N/A

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Deboer (2003)	The Netherlands	European Journal of Pharmacology	Review	Anxiety	Rodents	Shock-prod model	Abstract, Body of Text	361	In 1-3 sentences	No	N/A
Coenen (2003)	The Netherlands	Behavior Genetics	Review	Epilepsy	Rats	Genetic model	Abstract, Introduction, Body of Text	258	In 1-3 sentences	Yes	Yes
Haim (2003)	Israel	Psychopharmacology Bulletin	Review	Bipolar disorder	Not specified	Not specified	Abstract, Conclusion	71	4-10 sentences	Yes	Yes
Uys (2003)	South Africa	Current Psychiatry Reports	Review	Anxiety Disorders	Not specified	Not specified	Abstract, Introduction, Conclusion	70	In 1-3 sentences	No	N/A
Laviola (2003)	Italy	Neuroscience and Biobehavioral Reviews	Review	Not specified	Mice	Not specified	Abstract, Body of Text, Conclusion	504	In 1-3 sentences	No	N/A
Katz (2003)	USA	Psychopharmacology	Commentary	Drug addiction	Not specified	Reinstatement model	Body of Text	256	In 1-3 sentences	No	N/A
Ossenkopp (2003)	Canada	Behavioral Neuroscience	Original Research	Motion sickeness	Rats	Lithium chloride induced model	Abstract, Conclusion	37	In 1-3 sentences	No	N/A
Weiner (2003)	Israel	Psychopharmacology	Review	Schizophrenia	Rodents	Latent inhibition model	Abstract, Body of Text	404	In 1-3 sentences	No	N/A
Mayer (2002)	USA	Gastroenterological	Review	Gastrointestinal disorders	Not specified	Not specified	Body of Text	414	4-10 sentences	Yes	Yes
Kampen (2002)	Germany	Stress	Review	Depression	Tree Shrews	Chronic psychosocial stress paradigm model	Body of Text	105	4-10 sentences	Yes	Yes
Willner (2002)	UK	Behavioural Pharmacology	Review	Depression	Not specified	Not specified	Body of Text	467	10 or more sentences	Yes	Yes
Escobar (2002)	USA	Neuroscience & Biobehavioral Reviews	Review	Schizophrenia	Not specified	Not specified	Abstract, Introduction, Conclusion	88	In 1-3 sentences	No	N/A
Bourin (2001)	France	Human Psychopharmacology	Review	Depression	Not specified	Not specified	Abstract, Introduction	168	In 1-3 sentences	Yes	Yes
Weiss (2001)	Switzerland	Psychopharmacology	Review	Schizophrenia	Rats	Not specified	Abstract, Body of Text	228	4-10 sentences	No	N/A
Geyer (2001)	USA	Psychopharmacology	Review	Schizophrenia	Rats	Disrupted PPI models	Abstract, Body of Text, Conclusion	1510	4-10 sentences	No	N/A
Wolterink (2001)	The Netherlands	European Neuropsychopharmacology	Original Research	Neurodevelopmental disorders	Rats	Early amygdala damage model	Abstract, Conclusion	109	In 1-3 sentences	No	N/A
Overall (2000)	USA	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Psychiatric disorders	Canine	Not specified	Abstract, Body of Text, Conclusion	191	10 or more sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Moser (2000)	USA	Brain Research Reviews	Review	Schizophrenia	Not specified	Latent inhibition model	Abstract, Body of Text, Conclusion	237	4-10 sentences	Yes	Yes
Koob (2000)	USA	Addiction	Review	Alcohol Addiction	Not specified	Not specified	Body of Text	152	4-10 sentences	Yes	Yes
Sagvolden (2000)	Norway	Neuroscience and Biobehavioral Reviews	Review	Attention-Deficient Hyperactivity Disorder	Rats	Spontaneously Hypertensive Rat Model	Abstract, Body of Text, Conclusion	529	4-10 sentences	Yes	N/A
Yadid (2000)	Israel	Drug Development Research	Report	Depression	Rats	Flinders Sensitive Line	Abstract, Body of Text	16	In 1-3 sentences	Yes	Yes
Japha (1999)	Germany	Psychopharmacology	Original Research	Schizophrenia	Rats	Prepulse inhibition model	Abstract, Introduction, Discussion	89	4-10 sentences	No	N/A
Stolerman (1999)	UK	Behavioral Pharmacology	Review	Nicotine dependence	Not specified	Not specified	Abstract, Body of Text	61	4-10 sentences	Yes	Yes
Sams-Dodd (1999)	Denmark	Reviews in the Neurosciences	Review	Schizophrenia	Not specified	Not specified	Body of Text, Conclusion	162	10 or more sentences	Yes	Yes
Robbins (1998)	UK	Behavioral Pharmacology	Review	Cognitive disorders	Rats & monkeys	Not specified	Abstract, Introduction, Body of Text, Conclusion	64	4-10 sentences	Yes	Yes
Higgins (1998)	UK	Pharmacology and Pathophysiology	Review	Schizophrenia	Rodents	Not specified	Abstract, Introduction, Body of Text	5	In 1-3 sentences	Yes	Yes
Willner (1997)	UK	Psychopharmacology	Review	Depression	Not specified	Chronic stress model	Abstract, Body of Text, Conclusion	1937	10 or more sentences	Yes	No
Griebel (1996)	USA	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Review	Panic disorders	Not specified	Not specified	Abstract, Body of Text	79	In 1-3 sentences	Yes	Yes
D'Mello (1996)	UK	Cognitive Brain Research	Review	Cognitive disorders	Not specified	Not specified	Abstract, Body of Text	40	4-10 sentences	Yes	Yes
Jenck (1995)	Switzerland	Psychiatry research	Original Research	Panic Anxiety	Rats	Dorsal periaqueductal gray model	Abstract, Introduction, Discussion	215	In 1-3 sentences	Yes	Yes
Ellenbroek (1995)	The Netherlands	The Journal of Neuroscience	Original Research	Schizophrenia	Rats	Not specified	Title, Abstract, Introduction, Discussion	144	4-10 sentences	Yes	Yes
Porsolt (1995)	France	Drug Development Research	Review	Dementia	Not specified	Not specified	Body of Text	27	In 1-3 sentences	Yes	Yes

Author (Year)	Country	Journal/ Source article	Study Type	Medical Condition	Animal Species	Animal Model	Section CV mentioned	Number of citations	Frequency of CV	Definition Provided	Definition Cited
Swerdlow (1994)	USA	Archives of General Psychiatry	Review	Schizophrenia	Rats	PPI deficient model	Abstract, Body of Text	783	10 or more sentences	Yes	Yes
Markou (1993)	USA	Psychopharmacology	Review	Drug addiction	Not specified	Not specified	Body of Text	635	In 1-3 sentences	Yes	Yes
Overstreet (1993)	USA	Neuroscience and Biobehavioral Reviews	Review	Depression	Rats	Flinders Resistant Line	Abstract, Introduction, Body of Text, Conclusion	366	10 or more sentences	Yes	Yes
Moreau (1993)	Switzerland	Pharmacopsychiatry	Original Research	Depression	Rats	Chronic mild-stress induced model	Abstract, Introduction, Conclusion	54	In 1-3 sentences	Yes	Yes
Sarter (1992)	USA	Psychopharmacology	Review	Not specified	Not specified	Not specified	Body of Text, Conclusion	164	4-10 sentences	No	N/A
Willner (1992)	UK	Neuroscience and Biobehavioral Reviews	Review	Depression	Not specified	Chronic mild stress model	Abstract, Body of Text	810	4-10 sentences	Yes	No
Naitoh (1992)	Japan	The Keio Journal of Medicine	Original Research	Depression	Rats	Forced swim test model	Abstract, Discussion	23	In 1-3 sentences	Yes	Yes
Willner (1991)	UK	Animal Models in Psychiatry	Chapter	Psychopathology	Not specified	Not specified	Introduction, Body of Text	83	10 or more sentences	Yes	Yes
Joseph (1991)	UK	Behavioural Pharmacology	Commentary	Schizophrenia	Not specified	Not specified	Title, Abstract, Introduction	10	In 1-3 sentences	No	N/A
Ellenbroek (1990)	The Netherlands	Behavioural Pharmacology	Review	Not specified	Not specified	Not specified	Title, Abstract, Body of Text	258	10 or more sentences	Yes	Yes
Willner (1986)	UK	Progress in Neuro-Psychopharmacology and Biological Psychiatry	Review	Psychopathology	Not specified	Learned helplessness model	Abstract, Introduction, Discussion	355	10 or more sentences	Yes	No
Willner (1984)	UK	Psychopharmacology	Review	Depression	Not specified	Not specified	Abstract, Introduction, Body of Text, Conclusion	1460	10 or more sentences	Yes	No

Table 2. Summary Statistics of Study Characteristics

Study Characteristics (N=372)	Frequency (%)
Year of Publication	
2019 – 2016	137 (37%)
2015 – 2012	87 (23%)
2011 – 2008	77 (21%)
2007 – 2004	26 (7%)
2003 – 2000	22 (6%)
1999 – 1996	8 (2%)
1995 – 1992	10 (3%)
1991 – 1988	3 (0.8%)
1987 – 1984	2 (0.5%)
Country	
USA	126 (34%)
UK	30 (8%)
Canada	26 (7%)
The Netherlands	20 (5%)
Germany	18 (5%)
Brazil	18 (5%)
Italy	13 (3%)
Switzerland	13 (3%)
Japan	11 (3%)
Israel	11 (3%)
Other	86 (24%)
Study Type	
Review	191 (51%)
Original Research	127 (34%)
Chapter	18 (5%)
Reports/letters	17 (5%)
Editorial/Commentary	7 (2%)
Systematic Review	9 (2%)
Protocol	3 (1%)
Medical Condition/ Disease of Interest Classification*	
Neoplasms	3 (1%)
Cardiovascular system	3 (1%)
Certain infectious and parasitic diseases	2 (0.5%)
Digestive system	3 (1%)
Endocrine, nutritional and metabolic disease	2 (0.5%)
Mental and behaviour disorders	278 (75%)
Nervous system	49 (13%)
Congenital malformations, deformations and chromosomal abnormalities	4 (1%)
Injury, poisoning and certain other consequences of external causes	2 (0.5%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1 (0.3%)
Not specified	19 (5%)

***** Medical classification was categorized and defined using the International Statistical Classification of Disease – 10 list.

Table 3. Construct Validity Characteristics

Characteristics (N=372)	Frequency (%)
Definition of Construct Validity Provided	
Yes	225 (60%)
No	147 (40%)
Section in Article that Construct Validity was Mentioned (all that apply)	
Title	11 (3%)
Abstract	271 (73%)
Introduction	141 (38%)
Methods/Materials	14 (4%)
Results	9 (2%)
Discussion	89 (24%)
Body of text	199 (53%)
Conclusion	106 (28%)
Citation of Construct Validity Provided	
Yes	126 (34%)
No	89 (24%)
N/A	157 (42%)
Intensity of Construct Validity Presentation	
Term only	21 (6%)
1-3 sentences	174 (47%)
4-10	121 (32%)
More than 10 sentences	55 (15%)
Not mentioned (external validity mentioned)	1 (0.3%)
Was Construct Validity the Main Focus	
Yes	55 (15%)
No	317 (85%)
Provided Factors that Improve/Hinder Construct Validity	
Yes	82 (22%)
No	290 (78%)
Was external validity mentioned	
Yes	21 (6%)
No	351 (94%)
How was construct validity defined in comparison to external validity?	
Same as external validity	1 (0.3)
Separately from external validity	15 (4%)
Overlap between the two definitions	3 (0.8)
Did not define one or both terms	2 (0.5%)

Table 4. References of Construct Validity Definition

Reference	Number of Articles that Cited this Article
Willner (1984)	22
Willner (1991)	20
Willner (1986)	13
Geyer (1995)	7
Van der Staay (2006)	7
Van der Staay (2009)	6
Nestler (2010)	5
McKinney (1969)	5
Cronbach & Meehl (1955)	4
Ellenbroek (1990)	4
Belzung 2011	4
Henderson (2013)	3
Burrows (2011)	2
Fleming (2005)	2
Einat (2003)	2
Yadid (2000)	2
Walf & Frye (2007)	1
Belzung (2001)	1
Fendt (2005)	1
Van der Staay (2017)	1
Alonso (2015)	1
Sanchis-Segura (2006)	1
Duty & Jenner (2011)	1
Bronfeld (2013)	1
Jinnah & Hess (2005)	1
Davies (2012)	1
Ricceri (2008)	1
Katz (2012)	1
Katz (2003)	1
Samaco & Neul (2011)	1
Anacker (2010)	1
Kato (2007)	1
Goldstein (2011)	1
Kaluev (2006)	1
Sarkisov & Folomkina (2010)	1
Tricklebank (2012)	1
Lienert (1969)	1
Geyer (2000)	1
Treit (1985)	1
Menard (1999)	1
Borsboom (2004)	1
Mayer (2000)	1
Macho-Vieria (2004)	1
Crawley (2004)	1
Tkacs (2006)	1
Joel (2006)	1
Sayette (2000)	1
Willner (1992)	1
Iversen (1969)	1
Wuerbel (2017)	1

Table 5. Content Analysis Results

Author (Year)	Construct Validity Definition Quotes	Codes
Mack (2019)	The model must have similar behavioral manifestations as the human disease (construct validity)	Choice of model needs to match the human condition
Sonnenschein (2019)	Similar theoretical rationale, such as a common etiology	Choice of model supported by known theory
Qin (2019)	The construct validity refers to the degree of similarity between the experimental manipulation and the underlying causes of the human autism	Experimental conditions need to represent the human condition
Veening-Griffioen (2019)	Animal models can be compared to the human disease according to construct validity (the similarity in etiology)	Choice of model supported by known mechanism
Giorgi (2019)	Construct validity implies that the model has a sound theoretical rationale and heuristic potential, that is, it can aid in discovering novel characteristics of the modeled condition.	Choice of model backed up by known theory
Tadeven (2019)	Construct validity refers to how similarly the mutation in the model recapitulates the genetic state in the patients.	Choice of model supported by known mechanism
Zorkina (2019)	This criterion suggests that the modeled depression features should be unambiguously interpreted and regarded as homologous and should be related to depression both empirically and theoretically.	Choice of model supported by known theory Choice of model needs to match the human condition
Chadman (2019)	Construct validity refers to the animal model replicating the cause of a disease or disorder in humans.	Choice of model needs to match the human condition
Topal (2019)	Similarity in the basic underlying mechanism responsible for the condition in humans	Choice of model supported by known mechanism
Maximino (2019)	Construct validity usually refers to theories about etiology and pathogenesis, but can include other aspects that are related to the disorder, such as pharmacological isomorphism and ethological aspects	Choice of model supported by known theory
Miguel (2019)	A reliable animal model should mimic the mechanisms of the human disorder construct validity	Choice of model supported by known mechanism
Hmeljak (2019)	The gene target should have similar genetics and mechanism to the human disease gene and, if possible, should be an orthologue of the human gene	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Leffa (2019)	The second is construct validity, which can be evaluated by the similarity of pathophysiological mechanisms	Choice of model supported by known mechanism
Torok (2019)	Construct validity (called also pathological validity) is the theoretical rationale	Choice of model supported by known theory
Silva (2019)	Although many definitions of construct validity have been offered, its translational relevance is at least dependent on whether the model has a sound theoretical basis	Choice of model supported by known theory
Sena (2019)	'Construct validity' as the extent to which an outcome measure or experimental model measures what it purports to; We describe construct validity as the experimental demonstration of these similarities. Assessment of construct validity should take into account the animal model, the test or outcome measure and the attribute it is intended to measure	Choice of outcome measure needs to match the human condition
Yezierski (2019)	Models are truly representative of the human condition	Choice of model needs to match the human condition
Laeken (2019)	Construct validity is related to the resemblance in which the pathological changes that occur in patients with MDD, e.g., changes in the hypothalamic–pituitary–adrenal (HPA) axis, also occur in the animal.	Choice of model supported by known mechanism
Cenci (2018)	Construct validity can be defined as the demonstration that a model reproduces what it claims to be reproducing.	Model measures what it reports to
Pound (2018)	These failures of animal models to accurately represent human diseases and clinical contexts are sometimes described as failures of construct validity	Choice of model needs to match the human condition Experimental conditions need to represent the human condition
Kovacevic (2018)	Animal models with construct (same genetic cause of disease)	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Hart (2018)	Represents the degree of similarity with regard to pathophysiological mechanisms and symptoms between animal model and human disease	Choice of model needs to match the human condition Choice of model supported by known mechanism
Drozd (2018)	Construct validity refers to the model resembling the pathophysiology and etiology of the disorder, having risk factors for ASD such as a genetic mutation or developmental precedents. Construct validity refers to the model's reproducibility of clinical etiology and pathophysiology.	Choice of model supported by known mechanism
De La Pena (2018)	Construct validity concerns the similarity in etiology or underlying pathophysiological mechanism that induces the symptoms of the disorder	Choice of model supported by known mechanism
Ayuob (2018)	The pathophysiological changes that occur in patients with depression, such as changes in the HPA axis, hippocampal atrophy, and neurotransmitters must also occur in animals.	Choice of model supported by known mechanism
Robinson (2018)	Arises as a consequence of similar predisposing factors e.g. stress, genetic vulnerability, early life adversity	Choice of model needs to match the human condition
Winter (2018)	Construct validity in which the pathophysiological mechanisms underlying the behavior observed in animals are similar to those in the human conditions	Choice of model supported by known mechanism
Nicolini (2018)	Similarity in underlying causes	Choice of model needs to match the human condition
Morrice (2018)	Construct validity refers to how well the mechanism used to induce the disease phenotype in animals reflects what is currently understood to cause disease in patients. For example, how similar the genetic mutation is that causes pathology in animals to the mutation in disease patients.	Choice of model needs to match the human condition Choice of model supported by known mechanism
Rizzo (2018)	The rationale behind the model matches the pathological hypothesis	Choice of model supported by known theory
Paschoalin-Maurin (2018)	The structures that participate in the organization of defensive behaviors in rodents are exactly the same as those evoking fear in humans, providing a theoretical construct for our model	Choice of model supported by known theory

Author (Year)	Construct Validity Definition Quotes	Codes
Kristensen (2018)	The association between the Clock gene and BD (the construct validity of the ClockΔ19 mouse as a model for BD) is well established	Choice of model supported by known mechanism
Spanagel (2017)	As explained, these models have excellent face validity, and it is assumed that the neurochemical and neuroanatomical substrates involved in drug-intake behavior are similar in laboratory rodents and humans (which is often defined as construct validity).	Choice of model supported by known mechanism
McGraw (2017)	Construct validity refers to the similarity of etiologies of the disease and model.	Choice of model supported by known mechanism
Dekker (2017)	This study aimed to investigate the potential of DS mouse models (construct validity) in modelling the monoaminergic changes in DS	Choice of model supported by known mechanism
Farkas (2017)	The construct validity was successfully achieved in PACAP HZ mice by setting up the triple combination of factors according to the three-hit theory for major depression in humans	Choice of model supported by known theory
Commons (2017)	Construct validity is how well a test measures what it reports to measure	Model measures what it reports to
Vinner (2017)	Its construct validity is based on its similarity to the etiology of the pathological state	Choice of model supported by known mechanism
Liu (2017)	The reasonable theoretical rationales such as dysregulation of CORT and hippocampal BDNF insufficient	Choice of model supported by known theory
Vloo (2017)	A model has construct validity if it is based on a robust theoretical rationale. As opposed to face validity, depending on superficial resemblance, construct validity refers to underlying mechanisms or etiological similarities	Choice of model supported by known theory Choice of model supported by known mechanism
Bentea (2017)	Whether the model is induced in a manner that replicates pathogenic pathways relevant in the human disease	Choice of model supported by known mechanism
Nasuti (2017)	A criterion of construct validity is satisfied when the animal model shares the same underlying mechanism as the disease does	Choice of model supported by known mechanism
Zike (2017)	This is best understood in the context of genetic models, where a putative OCD risk gene is manipulated in mice to observe its behavioral and neurobiological consequences	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Van Kampen (2017)	While classic neurotoxin models, such as 6-OHDA and MPTP, mimic many of the biochemical features of PD, including reduced levels of striatal dopamine and tyrosine hydroxylase, they typically fail to replicate the accumulation of misfolded α-synuclein, the main component of Lewy bodies and Lewy neurites, another cardinal pathological feature of PD. In order for an animal model of PD to have good construct validity, it should display Lewy body-like α-synuclein inclusions.	Choice of model supported by known mechanism
Kanyuch (2017)	How well the model recapitulates a known or postulated etiologic process	Choice of model supported by known mechanism
Philippens (2017)	To model a disease, it is important for the construct validity, to have a degree of similarity between the mechanisms underlying the behavior in the model.	Choice of model supported by known mechanism
Yael (2016)	Construct validity refers to the theoretical rationale of the model, based on the known pathophysiology of the disorder	Choice of model supported by known theory Choice of model supported by known mechanism
Kostrzewa (2016)	Despite the fact that nigrostriatal damage is not an underlying pathophysiological process of human ADHD (i.e., lacking construct validity)	Choice of model supported by known mechanism
Humby (2016)	Briefly, acute postpartum inhibition of the steroid sulfatase enzyme in mouse mothers, predicted on the basis of theory to give rise to PP-related phenotypes ('construct validity')	Choice of model supported by known theory Choice of model needs to match the human condition
Reber (2016)	Construct validity refers to the psychoneuroendocrine/-immunologic bases of the disorder, trying to align the mechanisms of both the disorder itself and the disordered behavior exhibited by the model.	Choice of model supported by known mechanism
Veeraragavan (2016)	Although some loss-of-function Mecp2 mouse models of RTT have good construct validity and mimic either the human disease mutation itself or the consequence of the human disease-causing mutations	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Dirnagl (2016)	The most basic and dramatic threat to the validity of bench to-bedside translation concerns the question of whether preclinical models can predict human pathophysiology and therapeutic outcomes. This relates to the concept and construct validity of how we model the different types of strokes, and in a more general sense to whether nonhuman (in particular rodent) physiology and pathobiology are sufficiently similar to that of humans.	Choice of model supported by known mechanism
Mattina (2016)	Design elements aimed at maximizing the correspondence between experimental setup and clinical scenarios (construct validity)	Experimental conditions need to represent the human condition
Butler (2016)	The pathophysiological alterations that result in the human condition should also generate the relevant phenotypes in the animal model	Choice of model supported by known mechanism Choice of model needs to match the human condition
Ryabinin (2016)	The first study testing medications to decrease alcohol drinking had the goal of testing the construct validity of the prairie vole model. Such validation is based on the idea that if similar compounds decrease alcohol consumption in humans and in voles, then similar mechanisms must be involved in regulation of alcohol drinking in both species	Choice of model supported by known mechanism
Perrine (2016)	The construct validity of the mSPS model was assessed by multiple experimental approaches to determine if our model reflects the current, underlying conceptual theory of PTSD	Choice of model supported by known theory
Becker (2016)	Thus, animal models are most likely to have construct or predictive validity when the model mimics only the specific signs or symptoms associated with the psychopathological condition	Choice of model needs to match the human condition Choice of model supported by known mechanism
Hulbert (2016)	Construct validity, for our purposes, refers to the rationale behind the creation of the model and its ability to recapitulate the etiology of the disorder.	Choice of model supported by known theory Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Burrows (2016)	Construct validity involves recreating the etiologic processes that cause the human disorder in an animal model with the aim to reproduce neural and behavioural features of the illness. Construct validity in schizophrenia requires that the human mutations (or polymorphisms) are re-created as accurately as possible within the genomes of animal models. Similarly, construct validity might also be achieved through exposure of an animal to an environmental risk factor. Genetic construct validity refers to the extent to which the underlying composition of the model reflects the genetics of the disorder. The other major consideration with respect to animal models is environmental construct validity.	Choice of model supported by known mechanism Experimental conditions need to represent the human condition
Kostrzewa (2016)	Shared biological grounds with human conditions, such as mutation of a specific gene (construct validity)	Choice of model supported by known mechanism
Sharma (2016)	The 'construct validity', where we are in fact searching for its etiological validity at best (which is really only a component of construct validity. Similarity in the pathophysiological mechanisms presented by the model and the modeled condition, or the similarity of the biological processes that lead to disease. A validated model is expected to present biological alterations that are similar to those presented by patients	Choice of model supported by known mechanism
Cosgrove (2016)	An animal model that attempts to re-create any disease strives to maximize construct (i.e., etiologic), face, and predictive (i.e., pharmacologic) validities.	Choice of model supported by known mechanism
Kimmelman (2015)	Efficacy studies can fail clinical generalisation if investigators mischaracterise the relationship between a preclinical study and an ensuing trial. These mischaracterisations are called 'construct validity threats'. A researcher might mischaracterise a drug's utility for chronic human disease if it was tested only on animals during acute illness.	Experimental conditions need to represent the human condition Choice of model needs to match the human condition
Logan (2016)	Construct validity is the degree to which a test measures what it claims to measure. It often refers to the relevance or translational nature of the methods by which a model is constructed.	Model measures what it reports to
Mo (2016)	Construct validity is the degree to which the model matches the underlying mechanisms of the disease.	Choice of model supported by known mechanism
Kato (2016)	Construct validity refers to how the mechanism of a disease is shared between a disease and the model	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Godar (2016)	Based on this background, our findings collectively support the construct validity of this TS model. The pathophysiological relevance of D1CT-7 transgenic mice to TS symptoms is also supported by the recent discovery that TS patients display hyperactivity of the same sensorimotor circuit that is neuropotentiated in these mice; furthermore, it is worth noting that recent data indicated that in rodents the optogenetic stimulation of the cortex has been shown to produce features similar to symptoms of OCD – a highly co-morbid syndrome with TS.	Choice of model supported by known mechanism Choice of outcome measure needs to match the human condition
Fifel (2016)	The construct validity refers to the pathogenesis behind the disease	Choice of model supported by known mechanism
Foote (2016)	In order to accurately study the underlying biology, disease progression, and therapeutic effectiveness of uniquely human disorders, animal models should reflect as closely as possible how the disease manifests in patients. This is referred to as the construct validity for the model system. An important aspect of construct validity is that the model should reasonably mimic the molecular and cellular pathology of the disease that they were developed to model.	Choice of model supported by known mechanism Choice of outcome measure needs to match the human condition
Lalu (2016)	It has been suggested that failed preclinical to clinical translation may be related to a mismatch between experimental conditions and the clinical disease the model is intended to represent	Experimental conditions need to represent the human condition
Alonso (2015)	That the neural systems involved and the mechanism, whether physiological or psychological, underlying the behavioral symptoms observed in animals are similar to those responsible for the modeled disease (construct validity); An animal model is considered to show proper construct validity if the physiological or psychological mechanisms responsible for the behavioral symptoms observed in animals and the neural systems involved in them are similar to those known to be implicated in the human illness that is intended to be modeled.	Choice of model supported by known mechanism
Ruhela (2015)	Construct validity mainly relies upon the identity of causation between the animal phenotype and the human disease.	Choice of model supported by known mechanism
Henderson (2015)	A mismatch between experimental operations and the clinical scenario modeled (construct validity)	Experimental conditions need to represent the human condition

Author (Year)	Construct Validity Definition Quotes	Codes
Brunner (2015)	We believe that studying mouse models with robust construct validity is imperative, as they carry mutations that are found in humans with autism, even if these mice do not necessarily phenocopy human autism symptoms. Indeed, we did not expect the mouse models to recapitulate all of the autism domain deficits (to the extent that that is possible in a lower species); rather, we hoped to discover robust and consistent behaviors that may be useful for distinguishing the effects of treatment in future studies.	Choice of model supported by known mechanism Choice of outcome measure needs to match the human condition
Servadio (2015)	Construct validity refers to the theoretical rationale of the model – that is, similarity between the neurobiological mechanisms underlying the behavior in the model and those underlying the behavior in the pathological state that is being modeled.	Choice of model supported by known theory Choice of model supported by known mechanism
Mokoena (2015)	Construct (biology-related) validity	Choice of model supported by known mechanism
Varga (2015)	Compares the etiology of diseases in animal models and humans (construct validity)	Choice of model supported by known mechanism
Xu (2015)	How closely our model resembles the proposed theoretical construct of the human disease state	Choice of model supported by known theory
Perren (2015)	A model based on an established cause of the disease has construct validity and is useful in the understanding of the pathophysiological mechanism.	Choice of model supported by known mechanism
O'Connor (2015)	Construct validity refers to a similarity in underlying mechanisms even though the precise expression of behaviours may be different between animals and humans.	Choice of model supported by known mechanism
Bernard (2015)	Relationship of triggering mechanisms to human disease	Choice of model supported by known mechanism
Stewart (2015)	Relevance of the proposed model to disease etiology (mechanisms) in humans	Choice of model supported by known mechanism
Tyurenkov (2015)	Similarity in the physiological and neurochemical mechanisms between the model and the pathology causing the syndromal correspondence	Choice of model supported by known mechanism
Hirst (2014)	Recapitulation of human disease	Reflects the human condition

Author (Year)	Construct Validity Definition Quotes	Codes
Garner (2014)	Does the measure or model involve the mechanism or processes that is supposed to measure or model (at physiological, neuropsychological, motivational levels, etc.)? (For example, can the measure actually access these processes? Is the methodology consistent with the theory behind the measure? Does an animal model involve the same physiology as the human measure or condition?)	Choice of model supported by known mechanism Choice of outcome measure needs to match the human condition
Bey (2014)	The molecular defect mimics that seen in human ASD	Choice of model supported by known mechanism
McOmish (2014)	The gold standard for developing a mouse model of a human disorder has been to identify the aetiology, be it a genetic disruption (such as the tandem repeat expansion of the huntingtin gene in Huntington's disease) or environmental insult (such as traumatic brain injury), reproduce it in an animal model, and explore the pathology in order to develop novel treatment strategies.	Choice of model supported by known mechanism Choice of model needs to match the human condition
Weerasinghe (2014)	Construct validity refers to whether the induced pain condition in the animal model has similar underlying neurobiological mechanisms to the human clinical condition and was indicated by the occurrence of central sensitization, a key underlying mechanism of chronic pain, in the UVB/HR model	Choice of model supported by known mechanism
Bilkei-Gorzo (2014)	The same pathophysiological mechanism is responsible for the disease and for the phenotype in the model organism	Choice of model supported by known mechanism Choice of model needs to match the human condition
Pittman (2014)	Construct validity, i.e. whether disruption of a molecular mechanism known to be involved in learning and memory processes in mammals, would impair performance of zebrafish in this task	Choice of model supported by known mechanism
Kas (2014)	To address the point of construct validity, the clinically relevant prenatal rat VPA model and genetic mutant mouse models recapitulate many of these aspects, demonstrating the value of these models as well as the paradigms used to measure social behaviour in rodents	Choice of outcome measure needs to match the human condition Choice of model needs to match the human condition
McGonigle (2014)	Similar underlying biology	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
McGonigle (2014)	Requires the model to have similar underlying biology	Choice of model supported by known mechanism
Rezin (2014)	Construct validity refers to the similarity between mechanisms of the animal model and human disorder.	Choice of model supported by known mechanism
Abelaira (2013)	The pathophysiological changes that occur in patients with depression, such as changes in the HPA axis, hippocampal atrophy, and neurotransmitters must also occur in animals.	Choice of model supported by known mechanism
Gobira (2013)	Construct validity refers to how the model mimics the neurobiological mechanism of the disorder	Choice of model supported by known mechanism
Lauijssens (2013)	The animal model is based on a sound theoretical rationale, requiring good understanding of the human disease condition. Notably, construct validity does not require superficial similarity	Choice of model supported by known theory
Wolmarans (2013)	Construct validity was initially described by Geyer and Markou as the accuracy with which a certain test measures what it is intended to measure	Model measures what it reports to
Micale (2013)	Replicate the neurobiological abnormalities	Choice of model supported by known mechanism
Henderson (2013)	Construct validity concerns the degree to which inferences are warranted from the sampling particulars of an experiment (e.g., the units, settings, treatments, and outcomes) to the entities these samples are intended to represent.	Experimental conditions need to represent the human condition Model measures what it reports to
Vollmayr (2013)	Construct validity indicates that a model is based on mechanisms found to be important in the etiology and pathogenesis of major depression.	Choice of model supported by known mechanism
Moreira (2013)	Theoretical construct validity (homology)	Choice of model supported by known theory
Burrows (2013)	Construct validity in an animal model involves recreating the etiologic processes that cause the human disease and thus replicate neural and behavioral features of the illness.	Choice of model supported by known mechanism
Zemanova (2013)	Construct validity reflects the similarities between the real disease and the animal model in the pathogenesis and causes	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Marquez (2013)	The construct validity of the model is supported by the hallmark alterations of aggressive-impulsive behaviors in human subjects (that is, changes in the amygdala–MO cortex circuitry, the testosterone/corticosterone ratio53 and the serotonergic system41) that are recapitulated in our rat model	Choice of model supported by known mechanism
Vervliet (2013)	Construct validity refers to the disease relevance of the methods by which the model is constructed, with a focus on recreating the etiological process in the model. This requires an elaborated (etiological) theory of the disorder and of the model, and theoretical reasons to assume that the process in the model parallels the clinical process of interest.	Choice of model supported by known theory Choice of model supported by known mechanism
Lipina (2013)	Similarity of neurobiological mechanisms as in humans	Choice of model supported by known mechanism
Homberg (2013)	Construct validity of a test is defined as the accuracy with which the test measures similarities in underlying processes and etiologies of the phenomenon in animal and human behaviour.	Choice of model supported by known mechanism
Ciccocioppo (2013)	The pathology should be triggered by events thought to be important in eliciting the human disorder and should involve similar neurochemical, neurobiological and psychobiological mechanisms	Choice of model supported by known mechanism
Peleg-Raibstein (2012)	(Cronbach & Meehl): construct validity is involved whenever a test is to be interpreted as a measure of some attribute or quality which is not operationally defined.; Wilner & van der Staay: A narrower concept of construct validity is used to describe the degree of similarity between the mechanisms underlying the particular phenotype in the model and that underlying the phenotype in the condition which is being modeled. In the context of animal models of human brain disorders, construct validity is a theory-driven, experimental substantiation of the behavioral, pathophysiological, and/or neuronal elements of the model. Hence, it reflects the degree of fitting of the theoretical rationale and of modeling the true nature of the symptoms to be mimicked by the animal model.	Model measures what it reports to Choice of model supported by known theory Choice of model supported by known mechanism
Iderberg (2012)	The term construct validity reflects the working hypothesis that underlies the model, and whether the model is measuring what is intended.	Choice of model supported by known theory Model measures what it reports to

Author (Year)	Construct Validity Definition Quotes	Codes
Taneja (2012)	It is essential to mimic the pathophysiological changes that cause the overt symptoms	Choice of model supported by known mechanism
Modi (2012)	Construct validity, the model shares a common biological mechanism with the disorder; based on evolutionarily common neurobiological mechanisms; Model replicates etiological or neurobiological bases of the human condition being represented	Choice of model supported by known mechanism
Yanagi (2012)	In order to provide animal models with strong construct validity, we need to consider to what extent the model can reflect the putative essential biology of the human disease, using all available elements of forward and reverse translation to test this, once a construct has been formulated.	Choice of model supported by known mechanism
Albelda (2012)	Similarity in the mechanism (physiological or psychological) that induces behavioral symptoms and in the neural systems involved as contributing to construct validity	Choice of model supported by known mechanism
Koob (2012)	Construct validity refers to the interpretability, "meaningfulness," or explanatory power of each animal model and incorporates most other measures of validity in which multiple measures or dimensions are associated with conditions known to affect the construct. A procedure has construct validity if there are statistical or deterministic propositions that relate constructs (e.g., reward) to observables (e.g., thresholds) derived from the procedure. An alternative conceptualization of construct validity is the requirement that models meet the construct of functional equivalence, defined as "assessing how controlling variables influence outcome in the model and the target disorders.	Choice of outcome measure needs to match the human condition Experimental conditions need to represent the human condition
Parle (2012)	As the physiological and/or psychological causes of OCD are currently unknown, construct validity of animal modes of OCD can be established by demonstrating involvement of the serotonergic, dopaminergic and glutamatergic systems, the orbitofrontal cortex, cingulate cortex and basal ganglia, as well as by demonstrating modulation by ovarian hormones.	Choice of model supported by known mechanism
Sartori (2011)	Reveal mechanisms derived from theory	Choice of model supported by known mechanism Choice of model supported by known theory

Author (Year)	Construct Validity Definition Quotes	Codes
Honore (2011)	Construct validity is present when etiology and the underlying mechanism for pain are similar in humans and the animal	Choice of model supported by known mechanism
Freitas (2011)	Construct validity refers to commonalties between the mechanism of the model and of the human disorder	Choice of model supported by known mechanism
Belzung (2011)	'Whether both the behavior in the model (1) and the features of depression being modeled (2) can be unambiguously interpreted, and are homologous (3), and whether the feature being modeled stands in an established empirical (4) and theoretical (5) relationship to depression.' 'a theoretical account of the disordered behavior in the model, a theoretical account of the disorder itself, and a means to bring the two theories into alignment' 'Construct validity of a test is commonly defined as the accuracy with which the test measures what it is intended to measure' 'the accuracy with which the model measures what it is intended to measure' 'bring the theoretical accounts of both the disorder itself and the disordered behavior exhibited by the model into alignment' 'a theory-driven, experimental substantiation of the behavioral and/or neuronal components of the model (...) map a theory about the biopsychological mechanisms of a human disorder on to a biopsychotheory of a particular animal behavior'	Choice of model needs to match the human condition Choice of model supported by known theory Model measures what it reports to Choice of model supported by known mechanism
Trivedi (2011)	Construct validity refers to whether the designed model is able to deliver a relevant theoretical rationale for its performance.	Choice of model supported by known theory
Kluge (2011)	Construct validity is the case in which a model mimics the underlying molecular features of a disease along with patient characteristics or behavior	Choice of model supported by known mechanism
Fineberg (2011)	Similarity in underlying physiological or psychological mechanisms	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Zoratto (2011)	Limited construct validity (they fail to mimic the pathology in its aetiology)	Choice of model supported by known mechanism
Luyten (2011)	An animal model has construct validity if it is based on a robust theoretical rationale (wilner). construct validity refers to similarities in underlying mechanisms or etiology (Geyer)	Choice of model supported by known mechanism Choice of model supported by known theory
Patterson (2011)	Similar cause	Choice of model supported by known theory
Bari (2011)	Construct validity pertains to the theoretical status of the model	Choice of model supported by known theory
Vickers (2011)	An animal model of obesity will ideally mimic as closely as possible the human condition in terms of the causes of the disorder	Choice of outcome measure needs to match the human condition Choice of model supported by known mechanism
O'Connor (2011)	Construct validity refers to similarity in underlying mechanisms even though the precise expression of behaviours may be different between animals and humans.	Choice of model supported by known mechanism
Burrows (2011)	Construct validity refers to the accuracy of the model with respect to the specific human disorder being studied. Genetic construct validity is determined by how closely the gene mutation(s) in the animals match those of the disease-associated mutations/polymorphisms.	Choice of model supported by known mechanism
Neumann (2011)	Presupposes that a human disease and the animal model share common pathological substrates that can explain pathology in both, thereby enabling generation of a common mechanistic theory and experimental testing of the most salient clinical aspects of a given disease	Choice of model supported by known mechanism
Pryce (2011)	Construct validity i.e. the mouse—human face similarity must be underlain by similar psychological, physiological and neurobiological changes in the manipulated versus control mice and the MDD versus control human subjects	Choice of model supported by known mechanism
Scheggi (2011)	Thus, the behavioural modifications observed in cocaine-sensitized rats satisfy some requirements for an experimental model of anhedonia since they mimic an anhedonia-like symptom (construct validity)	Choice of model needs to match the human condition

Author (Year)	Construct Validity Definition Quotes	Codes
Wadenberg (2010)	Construct validity implies that the model has a sound theoretical rationale.	Choice of model supported by known theory
Varga (2010)	The model has a sound theoretical rationale	Choice of model supported by known theory
Sontag (2010)	Construct validity means that the model conforms to an established or hypothesized pathophysiological basis of the disorder.	Choice of model supported by known mechanism
Treit (2010)	Construct validity specifically addresses the question: "does the test or model actually measure or represent what it was intended to measure or represent?"	Model measures what it reports to
Shelley (2010)	This term refers to how well the condition of interest in the model represents the condition of interest in the target.	Model measures what it reports to
Wilson (2010)	The level of homology in pathological mechanisms (i.e., between the animal model and the human illness) that underlies disease symptoms is known as "construct validity."	Choice of model supported by known mechanism
Takumi (2010)	construct validity: similarity to the underlying causes of the disease	Choice of model supported by known mechanism
Klein (2010)	Construct validity requires a similarity in underlying mechanisms and/ or brain structures in the clinical situation and in the animal model.	Choice of model supported by known mechanism
Maximino (2010)	Construct validity refers to the "theoretical soundness" of animal models. The construct validity is not established by determining the relation between a test and an accepted criterion but is instead based on the establishment of relationships, which are in turn based on the definition of a trait. Implicitly, a construct is defined by a network of associations.	Choice of model supported by known theory
Duman (2010)	The extent to which they model the true disease process or its etiology in humans (construct or etiologic validity)	Choice of model supported by known mechanism
Radyushkin (2010)	As it is debatable which constructs are central in the pathophysiology of schizophrenia, animal models with convincing construct validity (e.g. Willner 1986) have been sparse	Choice of model supported by known mechanism
Inagaki (2010)	Construct validity—that brain structures processing and/or inducing these anxiety-related changes should be the same in the animal model and in humans	Choice of model supported by known mechanism
Jornada (2010)	Share pathophysiological characteristics of the human condition	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Meyer (2010)	This refers to the degree of similarity between the mechanisms underlying the particular phenotype in the model and that underlying the phenotype in the condition which is being modeled. Hence, construct validity accounts for mechanistic similarities between the model and the clinical condition. Hence, it reflects the degree of fitting of the theoretical rationale and of modeling the true nature of the symptoms to be mimicked by the animal model.	Choice of model supported by known mechanism Choice of model supported by known theory
Young (2010)	Construct validity is most commonly defined as the accuracy with which the test measures that which it is intended to measure	Model measures what it reports to
van der Staay (2009)	According to Epstein construct validity points to the degree of similarity between the mechanisms underlying behavior in the model and that underlying the behavior in the condition, which is being modeled. Construct validity thus is a theory-driven, experimental substantiation of the behavioral, pathophysiological, and/or neuronal components of the model, i.e. it reflects the degree of fitting the theoretical rationale and of modeling the true nature of the symptoms/syndrome to be mimicked by the animal model.	Choice of model supported by known mechanism Choice of model supported by known theory
Lu (2009)	Construct validity requires that the animal model shared the same etiology and underlying pathophysiological mechanisms as seen in human disease	Choice of model supported by known mechanism
Boulougouris (2009)	Construct validity means that the model should be logical in itself and is based a) on the degree of functional homology between the modelled behavior and the behavior in the model which depends on the two behaviors sharing a similar physiological basis, and b) on the significance of the modelled behavior in the clinical setting	Choice of model supported by known mechanism
Takeda (2009)	How well the model is consistent with the theoretical rationale. Construct validity refers to commonalities between the mechanisms of the model and those of the human disorder	Choice of model supported by known theory Choice of model supported by known mechanism
Ashkenazy (2009)	Possible shared underlying mechanisms	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Malkesman (2009)	Construct validity is the most complex of these three terms; loosely defined, it essentially reflects the degree to which a model measures what it claims to be measuring, and it allows researchers to generate a possible common mechanistic theory that can explain both the animal model and the human disorder	Model measures what it reports to Choice of model supported by known mechanism
Morsink (2009)	The extent to which the model mimics the disease by shared etiology and underlying pathophysiological mechanisms; Overlap in underlying etiology and pathophysiology between the disease and animal model is clearly described	Choice of model supported by known mechanism
O'Dell (2009)	Is the theoretical premise underlying human nicotine addiction similar to that in the animal model?	Choice of model supported by known theory
Markou (2008)	Construct validity, defined as measuring accurately the theoretical behavioral and neurobiological variables that are considered core to the disorder of interest	Choice of model supported by known theory
Sagvolden (2008)	Conform to a theoretical rationale for ADHD (construct validity)	Choice of model supported by known theory
Schmidt (2008)	The term construct validity implies that the model is based on a solid theoretical and scientific rationale.	Choice of model supported by known theory
Gerlach (2008)	Construct validity conforms to a theoretical rationale for the disease	Choice of model supported by known theory
Kasahara (2008)	But such models hardly satisfy the construct validity; that is, these animals do not mimic aspects of the etiology	Choice of model supported by known mechanism
Herman (2007)	Construct validity, the pathogenesis of the behavioral abnormalities must be the same as, or at least similar to, the human condition	Choice of model supported by known mechanism
Maccari (2007)	Construct validity represents the degree to which both the human syndrome and the animal model are unambiguously defined such that a rational theory can be constructed to explain the pathophysiology of disorder	Choice of model supported by known mechanism Choice of model supported by known theory
Kato (2007)	Construct validity refers to commonalties between the mechanism of the model and of the human disorder.	Choice of model supported by known mechanism
Sarter (2006)	An approach designed to determine the degree to which an animal model incorporates relationships between multiple levels of analysis as proposed by theory.	Choice of model supported by known theory

Author (Year)	Construct Validity Definition Quotes	Codes
McArthur (2006)	Construct validity is closely related to the pathology and symptomatology of the disorder, and the accuracy with which changes in the model organism reflects that in the human.	Choice of model supported by known mechanism Choice of model needs to match the human condition
Swerdlow (2006)	To demonstrate construct validity, the theoretical rationale behind the model must be consistent with what is known about the "pathophysiologic construct" of the disorder in humans.	Choice of model supported by known theory Choice of model supported by known mechanism
Van der Staay (2006)	Construct validity refers to the theoretical clarification of what a test measures and is the most important aspect of validity as far as animal models are considered. Animal models possess construct validity if their procedures are theoretically sound. The construct validity is not established by determining the relation between a test and an accepted criterion but is instead based on the establishment of relationships, which are in turn based on the definition of a trait. Implicitly, a construct is defined by a network of associations	Choice of model supported by known theory
Frey (2006)	Construct validity is related to the ability of the model to reproduce some pathophysiological aspects of the illness	Choice of model supported by known mechanism
Joel (2006)	Construct validity means that the model has a sound theoretical rationale, and depends on the degree of homology between the behavior that is being modeled and the behavior in the model (two behaviors are considered homologous if they share a similar physiological basis), and on the significance of the modeled behavior in the clinical picture	Choice of model supported by known theory Choice of model supported by known mechanism
Winston (2005)	In general, the utility of an animal model of disease may be assessed based on its construct validity (consistence with a particular theoretical rationale behind its development)	Choice of model supported by known theory
Swerdlow (2005)	Construct validity is achieved by an animal model when the theoretical rationale behind the model is consistent with what is known about the pathophysiology of the disorder in humans	Choice of model supported by known theory Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Sagvolden (2005)	Construct validity conforms to a theoretical rationale for the disorder	Choice of model supported by known theory
Anisman (2005)	At the very least, animal models must resemble the human condition in several respects, including [...] (d) involvement of similar neurochemical processes (construct validity)	Choice of model supported by known mechanism
Barr (2005)	Construct validity in which the behavioral changes in the animal model must be homologous, or at least analogous, to the symptoms of the disorder; construct validity (defined as the precision with which the model measures that which it is designed to measure)	Choice of model needs to match the human condition Model measures what it reports to
Lubow (2005)	Construct validity refers to the degree to which a set of related procedures generates data that reflect the essential process that those procedures purport to assess. As such, there are two critical aspects of construct validity, the relationships of the manipulations (independent variables) and of the measurements (dependent variables) to the theoretical hypotheses that are being tested. Consequently, one cannot talk about the construct validity of a particular animal model of psychopathology without first specifying the core process that is postulated to be common to the model and to the disorder	Choice of model supported by known theory Choice of model supported by known mechanism
Fuchs (2005)	Homology and similarity in the underlying neurobiological mechanisms	Choice of model supported by known mechanism
Crawley (2004)	Construct validity, i.e., similarity to the underlying causes of the disease	Choice of model supported by known mechanism
Corwin (2004)	The theoretical rationale upon which they are based	Choice of model supported by known theory
Coenen (2003)	The model should have a sound theoretical rationale and construct	Choice of model supported by known theory
Haim (2003)	Construct validity represents a possible common mechanistic theory that can explain both the model and the modeled disorder	Choice of model supported by known mechanism
Mayer (2002)	If the model is consistent with a particular theoretical rationale	Choice of model supported by known theory
Kampen (2002)	Assesses to what extent the model is consistent with the theoretical rationale	Choice of model supported by known theory

Author (Year)	Construct Validity Definition Quotes	Codes
Willner (2002)	Construct validity implies that the model has a sound theoretical rationale	Choice of model supported by known theory
Bourin (2001)	Does the model possess a strong theoretical rationale	Choice of model supported by known theory
Overall (2000)	Construct validity where the model either relies on or elucidates the same basic underlying mechanism responsible for the condition in humans. A homologous model (e.g., true construct validity; a model that implies that the "cause" of the behavioral response in the animal is sufficient to provoke the same response in humans)	Choice of model supported by known mechanism
Moser (2000)	Similar underlying neurophysiological concept, such as the postulated role of selective attention deficits in both schizophrenia and in LI)	Choice of model supported by known mechanism
Koob (2000)	Accuracy with which behavior in an animal model measures what it is intended to measure	Model measures what it reports to
Sagvolden (2000)	Conforms with a theoretical rationale for the disorder	Choice of model supported by known theory
Yadid (2000)	How well the model is consistent with theoretical rationale	Choice of model supported by known theory
Stolerman (1999)	Construct validity is based on the theoretical underpinning of the model system	Choice of model supported by known theory
Sams-Dodd (1999)	The level of construct validity has been referred to as the theoretical rationale of the model by Willner et al. and Ellenbroek and Cools have likewise included theoretical considerations in their definition of this criterion.	Choice of model supported by known theory
Robbins (1998)	Construct validity refers to the identification of common basic behavioral processes mediated by neural and neurochemical systems that derive from common ontogenetic and phylogenetic origins.	Choice of model supported by known mechanism
Higgins (1998)	The model should show a similar underlying neurobiology as the disorder	Choice of model supported by known mechanism
Willner (1997)	A sound theoretical rationale	Choice of model supported by known theory
Griebel (1996)	Construct validity implies that the cause of behavioral change in the animal is sufficient to cause a similar response in man	Choice of model needs to match the human condition

Author (Year)	Construct Validity Definition Quotes	Codes
D'Mello (1996)	Construct validity indicates how well the measure of a particular process reflects theoretical assumptions about that process.	Choice of model supported by known theory
Jenck (1995)	Construct validity, which addresses the theoretical rationale of the model and usually includes etiological, neurophysiological, and neuropathological aspects of the disorder. Construct validity is another important validation aspect dealing with the theoretical rationale underlying the model (Willner, 1986, 1990) including etiological, neurophysiological, and neuropathological aspects of the disorder.	Choice of model supported by known theory Choice of model supported by known mechanism
Ellenbroek (1995)	Models in which the psychopathological construct of the disease is modeled	Choice of model supported by known mechanism
Porsolt (1995)	A fundamental requirement of this approach is that the model correspond as closely as possible to all that is known about the clinical condition.	Choice of model needs to match the human condition
Swerdlow (1994)	A model has construct validity if it demonstrates both empirical and theoretical consistency with a proposed physiological construct, related either to the cause of a disorder or to the therapeutic mechanism of drug action.	Choice of model supported by known theory Choice of model supported by known mechanism
Markou (1993)	Scientific definition of a theoretical construct requires that the construct is part of a nomothetic span (i.e., theoretical framework; Cronbach and Meehl 1955; Embretson 1983) and is defined operationally (Bridgman 1945; Feigl 1945).	Choice of model supported by known theory
Overstreet (1993)	One can then assess how well the particular model or class of model is consistent with some sound theoretical rationale, i.e., has construct validity	Choice of model supported by known theory
Moreau (1993)	Should model a core symptom of the disorder (construct validity) preferably with a prolonged time course	Choice of model needs to match the human condition
Naitoh (1992)	Construct validity; clinical and experimental evidence suggests the strong relationship between stress and depression .	Experimental conditions need to represent the human condition
Ellenbroek (1990)	Consturct validity: (1) the essential feature(s) in the model and schizophrenia should be unambiguously interpretable; (2) the feature(s) being modelled should stand in an established empirical relationship to schizophrenia; (3) the feature(s) being modelled should stand in an established theoretical relationship to schizophrenia	Choice of model supported by known theory Choice of model needs to match the human condition

Author (Year)	Construct Validity Definition Quotes	Codes
Willner (1986)	Construct validity concerns its theoretical rationale	Choice of model supported by known theory
Willner (1984)	Construct validity is assessed by whether both the behaviour in the model (1) and the features of depression being modelled (2) can be unambiguously interpreted, and are homologous (3), and whether the feature being modelled stands in an established empirical (4) and theoretical (5) relationship to depression.	Choice of model supported by known theory Choice of model needs to match the human condition
Willner (1991)	Means that the model has a sound theoretical rationale	Choice of model supported by known theory
Maximino (2010)	In validation research, construct validity can be defined as an ontological statement about a property of some test which defines the test as valid for measuring an attribute if (a) the attribute exists and (b) variations in the attribute causally produce variation in the measurement outcomes	Choice of outcome measure needs to match the human condition Model measures what it reports to
McNaughton (2008)	‘‘Construct validity’’ is conferred on animal models ‘‘if their procedures are theoretically sound. The construct validity is not established by determining the relation between a test and an accepted criterion but is instead based on the establishment of relationships, which are in turn based on the definition of a trait. Implicitly, a construct is defined by a network of associations’’.	Choice of model supported by known theory
Wurbel (2017)	Assessment of construct validity should be based on evidence about the level of agreement between the animal model, test or outcome variable and the quality it is meant to measure	Choice of outcome measure needs to match the human condition Model measures what it reports to
Grone (2015)	These animals should recapitulate the causal mechanism(s) underlying the disease in humans	Choice of model supported by known mechanism
Willner (1992)	Construct validity refers to the theoretical rationale for the model	Choice of model supported by known theory
Yang (2011)	Construct validity refers to the similarity of the genetic context used to develop the mouse model to that found in HD patients	Choice of model supported by known mechanism
Castagné (2009)	For construct validity, the animal procedure must reproduce etiological factors of the disease.	Choice of model supported by known mechanism

Author (Year)	Construct Validity Definition Quotes	Codes
Miczek (2013)	The most valuable models achieve homology between the experimental preparation and cardinal symptoms of the clinical condition in terms of phylogenetic and ontogenetic origins (construct validity)	Choice of model needs to match the human condition
Risbrough (2008)	Construct validity of a model is defined as the accuracy with which the test measures what it is intended to measure	Model measures what it reports to
Lalu (2014)	Construct validity in preclinical research concerns the extent to which an experimental system accurately models a clinical entity.	Experimental conditions need to represent the human condition
Suen (2016)	Construct validity in preclinical research refers to the ability of a study to generalizable to a clinical scenario	Experimental conditions need to represent the human condition Choice of model needs to match the human condition
Kalueff (2004)	Based on similar theoretical rationale (homology) behind the pathology in animals and humans.	Choice of model supported by known theory
Uilenreef (2019)	Construct validity refers to the legitimacy of either the experimental manipulations used or the measurements that are performed in a model to assess a certain aspect of the condition.	Experimental conditions need to represent the human condition Choice of outcome measure needs to match the human condition
Valvassori (2019)	Construct validity, showing the ability of the model to simulate pathophysiological aspects of the illness	Choice of model supported by known mechanism

Table 6. Content Analysis Codebook

Code	Definition of Code	Example	Frequency of Code (n)
Choice of model supported by known theory	Based on a proposed cause, theory, or underlying principle of disease.	"The construct validity of the mSPS model was assessed by multiple experimental approaches to determine if our model reflects the current, underlying conceptual theory of PTSD"	71
Choice of model supported by known mechanism	Accounts for mechanism of action or cause of disease (i.e., physiology, chemistry, biology, genes, pathophysiology, etiology etc.).	"A criterion of construct validity is satisfied when the animal model shares the same underlying mechanism as the disease does"	136
Choice of model needs to match the human condition	Preclinical model chosen or justified by researchers to recapitulate the clinical condition through the phenotype (i.e., observable characteristics or appearances), but does not consider the mechanism of action of the disease.	"The model must have similar behavioral manifestations as the human disease"	27
Choice of outcome measure needs to match the human condition	Outcomes and endpoints chosen or justified by researchers to recapitulate the clinical condition.	"'Construct validity' as the extent to which an outcome measure or experimental model measures what it purports to"	11
Experimental conditions need to represent the human condition	Aspects of experimental design chosen or justified by researchers to recapitulate the clinical condition.	"Design elements aimed at maximizing the correspondence between experimental setup and clinical scenarios"	13
Model measures what it reports to	Simplified definitions of construct validity that does not mention what part of the model researchers are interested in matching to the human condition, but rather the construct of interest.	"Construct validity is the degree to which a test measures what it claims to measure. It often refers to the relevance or translational nature of the methods by which a model is constructed."	17

Appendix B - Figures

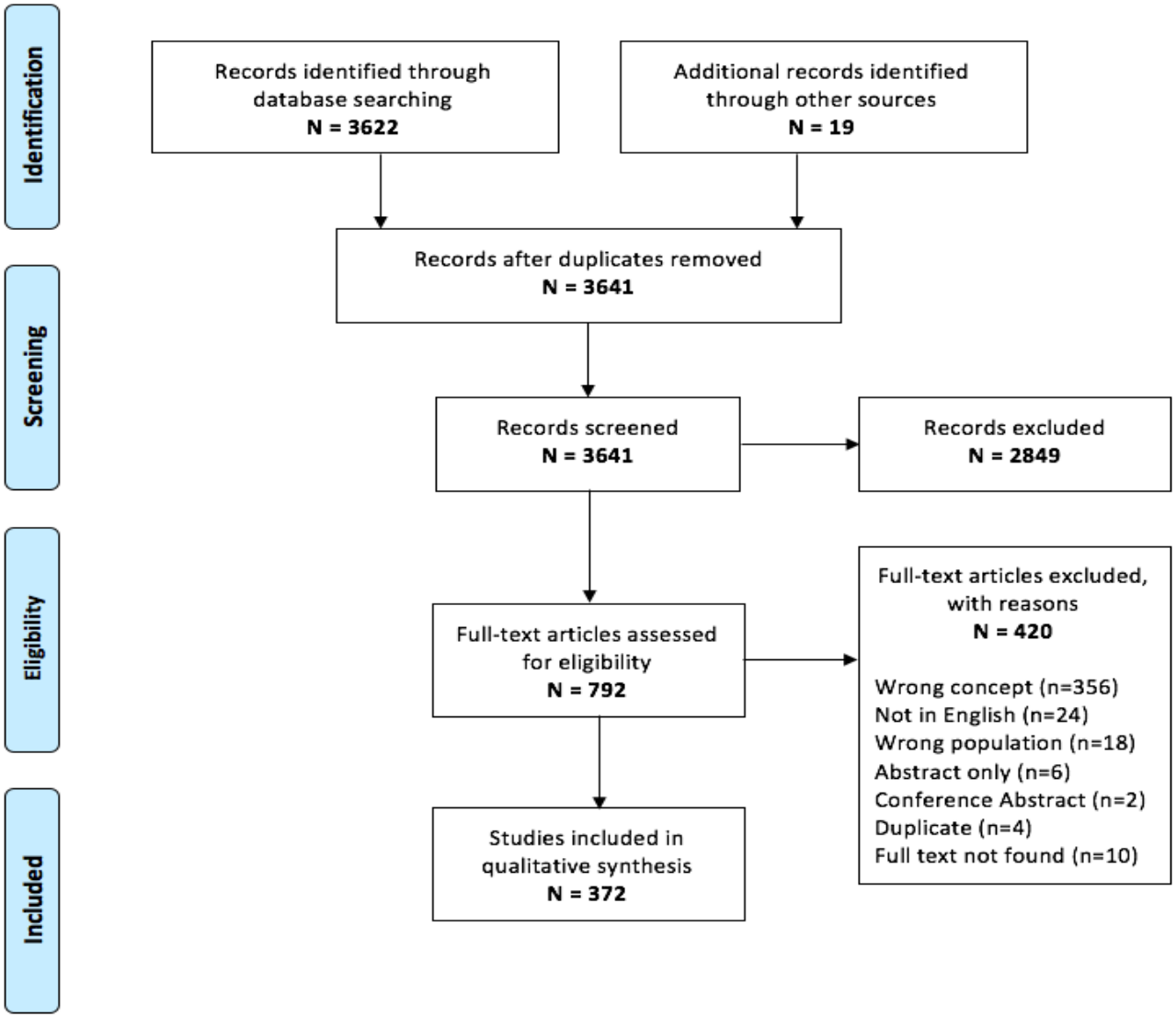

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Chart Diagram

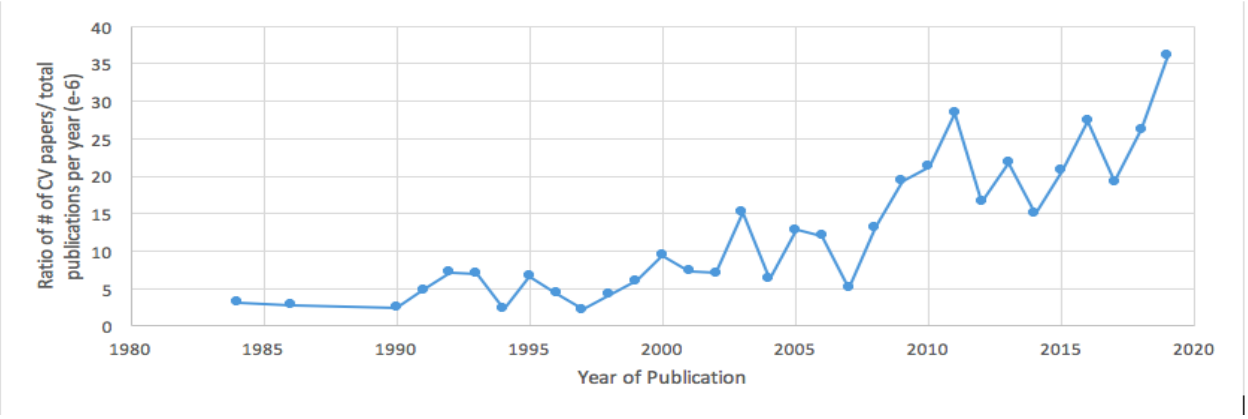

Figure 2. Normalized Data for Number of Articles on Construct Validity Published per Year

Appendix C – Search Strategy

Database: Embase Classic+Embase <1947 to 2019 October 10>, Ovid MEDLINE(R) ALL <1946 to October 10, 2019>
Search Strategy:
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1 exp animals/ not humans/ (18720492)
2 (animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat or murinae or muridae or cottonrat or cottonrats or hamster or hamsters or cricetinae or rodentia or rodent or rodents or pigs or pig or swine or swines or piglets or piglet or boar or boars or "sus scrofa" or ferrets or ferret or polecat or polecats or "mustela putorius" or "guinea pigs" or "guinea pig" or cavia or callithrix or marmoset or marmosets or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys or anthropoidea or anthropoids or saguinus or tamarin or tamarins or leontopithecus or hominidae or ape or apes or pan or paniscus or "pan paniscus" or bonobo or bonobos or troglodytes or "pan troglodytes" or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or "bush baby" or prosimian or bush babies or galagos or galago or pongidae or gorilla or gorillas or pongo or pygmaeus or "pongo pygmaeus" or orangutans or pygmaeus or lemur or lemurs or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs or bombina or salientia or toad or toads or "epidalea calamita" or salamander or salamanders or eel or eels or fish or fishes or pisces or catfish or catfishes or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or trout or trouts or char or chars or salvelinus or "fathead minnow" or minnow or cyprinidae or carps or carp or zebrafish or zebrafishes or goldfish or goldfishes or guppy or guppies or chub or chubs or tinca or barbels or barbus or pimephales or promelas or "poecilia reticulata" or mullet or mullets or seahorse or seahorses or mugil curema or atlantic cod or shark or sharks or catshark or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or "sea lamprey" or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or xenopus laevis or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or "wild hog" or "wild boar" or fitchew or fitch

or beaver or beavers or jerboa or jerboas or capybara or capybaras).tw,kf. (10734843)
3 exp models, animal/ (1866057)
4 ((pre clinic* or preclinic*) adj2 model*).tw. (46704)
5 Animal Experimentation/ (2455953)
6 (preclinic* or pre clinic*).ti. (42428)
7 or/1-6 (21931454)
8 (construct and validity).tw,kf. (51176)
9 (external and validity).tw,kf. (16211)
10 model* validity.tw,kw. (847)
11 (predict* adj2 validity).tw. (15596)
12 (predict* and validity).kf. (225)
13 clinical inference.tw,kw. (188)
14 *Translational Medical Research/ (10067)
15 (translational adj2 research).ti. (5728)
16 or/8-15 (92214)
17 7 and 16 (31584)
18 17 use medall (3082) Medline
19 exp *animal/ not human/ (1950977)
20 (animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat
or murinae or muridae or cottonrat or cottonrats or hamster or hamsters
or cricetinae or rodentia or rodent or rodents or pigs or pig or swine or swines or piglets or piglet
or boar or boars or "sus scrofa" or ferrets or ferret or polecat or polecats or "mustela putorius" or
"guinea pigs" or "guinea pig" or cavia or callithrix or marmoset or marmosets
or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or
jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly
or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode
or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines
or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat
or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys
or anthropoidea or anthropoids or saguinus or tamarin or tamarins
or leontopithecus or hominidae or ape or apes or pan or paniscus or "pan paniscus" or bonobo or
bonobos or troglodytes or "pan troglodytes" or gibbon or gibbons or siamang or siamangs
or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or "bush baby" or
prosimian or bush babies or galagos or galago or pongidae or gorilla or gorillas or pongo
or pygmaeus or "pongo pygmaeus" or orangutans or pygmaeus or lemur or lemurs
or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens
or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile
or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile
or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs
or bombina or salientia or toad or toads or "epidalea calamita" or salamander or salamanders or
eel or eels or fish or fishes or pisces or catfish or catfishes
or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or
trout or trouts or char or chars or salvelinus or "fathead minnow" or minnow or cyprinidae or
carps or carp or zebrafish or zebrafishes or goldfish or goldfishes or guppy or guppies or chub or
chubs or tinca or barbels or barbus or pimephales or promelas or "poecilia reticulata" or mullet or
mullets or seahorse or seahorses or mugil curema or atlantic cod or shark or sharks or catshark

or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or "sea lamprey" or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or xenopus laevis or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or "wild hog" or "wild boar" or fitchew or fitch or beaver or beavers or jerboa or jerboas or capybara or capybaras).tw. (10685625)

21 exp *animal model/ or animal model/ (1508123)
22 ((pre clinic* or preclinic*) adj2 model*).tw. (46704)
23 *animal experiment/ (9525)
24 (preclinic* or pre clinic*).ti. (42428)
25 19 or 20 or 21 or 22 or 23 or 24 (11617917)
26 construct validity/ (13493)
27 construct validity.tw. (39605)
28 external validity/ (4142)
29 external validity.tw. (8225)
30 model* validity.tw. (826)
31 (predict* adj2 validity).tw. (15596)
32 clinical inference.tw. (182)
33 *translational research/ (12030)
34 (translational adj2 research).ti. (5728)
35 or/26-34 (82394)
36 25 and 35 (6384)
37 conference.pt. (4385112)
38 conference.so. (496483)
39 36 not (37 or 38) (4863)
40 39 use emczd (2345) Embase
41 18 or 40 (5427)
42 remove duplicates from 41 (3652)
43 42 use medall (3077) Medline
44 42 use emczd (575) Embase

Appendix D – PRESS Review Search Strategy

PRESS Guideline — Search Submission & Peer Review Assessment
SEARCH SUBMISSION: THIS SECTION TO BE FILLED IN BY THE SEARCHER

Searcher's Name: Risa Shorr Email: rshorr@toh.ca
Date Submitted: 2019-10-09

1. Systematic Review Title
Not sure

2. This search strategy is: (Highlight the appropriate response)

A. My PRIMARY (core) database strategy — First time submitting a strategy for search question and database

B. My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

C. SECONDARY search strategy— First time submitting a strategy for search question and database

D. SECONDARY search strategy – NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions.

3. Database (ie, Medline, Cinahl)
Medline

4. Interface (Ovid, Ebsco)
Ovid

5. Research Question. Describe the purpose of the search
External construct validity in preclinical research

6. PICO Format (Outline the PICOs for your question – ie. Patient, Intervention, Comparison, Outcome and Study Design – as applicable)

P	Preclinical research
I	External construct validity
C	
O	

Inclusion Criteria (List criteria such as age groups, study designs, etc, to be included) [optional]
Exclusion Criteria (List criteria such as study designs, date limits, etc., to be excluded) *[optional]*

7. Was a search filter applied?

No

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. [mandatory if YES to previous question — textbox]

Other notes or comments you feel would be useful for the peer reviewer? [optional]

Target references
30953144
26463620
25541540
20934650
20361020

8. Please copy and paste your search strategy here, exactly as run, including the number of hits per line. [mandatory]
Database: Ovid MEDLINE(R) ALL <1946 to October 08, 2019>
Search Strategy:
---
1 exp animals/ not humans/ (4626413)
2 (animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat or murinae or muridae or cottonrat or cottonrats or hamster or hamsters or cricetinae or rodentia or rodent or rodents or pigs or pig or swine or swines or piglets or piglet or boar or boars or "sus scrofa" or ferrets or ferret or polecat or polecats or "mustela putorius" or "guinea pigs" or "guinea pig" or cavia or callithrix or marmoset or marmosets or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys or anthropoidea or anthropoids or saguinus or tamarin or tamarins or leontopithecus or hominidae or ape or apes or pan or paniscus or "pan paniscus" or bonobo or bonobos or troglodytes or "pan troglodytes" or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or "bush baby" or prosimian or bush babies or galagos or galago or pongidae or gorilla or gorillas or pongo or pygmaeus or "pongo pygmaeus" or orangutans or pygmaeus or lemur or lemurs or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs or bombina or salientia or toad or toads or "epidalea calamita" or salamander or salamanders or eel or eels or fish or fishes or pisces or catfish or catfishes or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or trout or trouts or char or chars or salvelinus or "fathead minnow" or minnow or cyprinidae or carps or carp or zebrafish or

zebrafishes or goldfish or goldfishes or guppy or guppies or chub or chubs or tinca or barbels or barbus or pimephales or promelas or "poecilia reticulata" or mullet or mullets or seahorse or seahorses or mugil curema or atlantic cod or shark or sharks or catshark or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or "sea lamprey" or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or xenopus laevis or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or "wild hog" or "wild boar" or fitchew or fitch or beaver or beavers or jerboa or jerboas or capybara or capybaras).tw,kf. (4738199)
3 exp models, animal/ (546834)
4 ((pre clinic* or preclinic*) adj2 model*).tw. (16573)
5 Animal Experimentation/ (4186)
6 (preclinic* or pre clinic*).ti. (16299)
7 or/1-6 (6232466)
8 (construct and validity).tw,kf. (23278)
9 (external and validity).tw,kf. (7191)
10 model* validity.tw,kw. (369)
11 (predict* adj2 validity).tw. (7017)
12 (predict* and validity).kf. (225)
13 clinical inference.tw,kw. (87)
14 *Translational Medical Research/ (5500)
15 or/8-14 (41061)
16 7 and 15 (2780)

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: Sascha Davis Email: adavis@toh.ca Date Completed: Click or tap here to enter text.

9. Translation
A- No Revision

If "B' or "C", please provide and explanation or example

10. Boolean and Proximity Operators
A- No Revision

If "B' or "C", please provide and explanation or example

11. Subject Headings
A- No Revision

If "B' or "C", please provide and explanation or example

12. Text Word Searching
A- No Revision

If "B' or "C", please provide and explanation or example

13. Spelling, Syntax and Line Numbers
A- No Revision
If "B' or "C", please provide and explanation or example

14. Limits and Filters
A- No Revision
If "B' or "C", please provide and explanation or example
Overall Evaluation

Additional Comments: Overall good. I left some comments by the strategy.

Appendix E – PRISMA Checklist

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Pg. 20
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Pg. 22
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Pg. 23 – 24
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Pg. 24
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Pg. 24 – 25
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Pg. 26
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Pg. 25 – 26
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix C (pg. 149 – 151)
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Pg. 26

Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Pg. 26 – 27
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Pg. 27 – 28
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not applicable
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Pg. 28
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Pg. 28 Appendix B (pg. 147)
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Pg. 29
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendix A (pg. 94 – 146)
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Pg. 30 – 32
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 32 – 35
Limitations	20	Discuss the limitations of the scoping review process.	Page 35
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 45

FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 36

Chapter 4. An Overview of Preclinical Systematic Reviews Protocol: Identifying Key Characteristics and Prevalence of Construct Validity

Preface:

This chapter outlines the protocol for the overview of systematic reviews, which has been registered on the Open Science Framework. Rania Berjawi drafted the initial protocol and created the data extraction forms. Drs. Fergusson, Lalu, and Brehaut provided input and revision on all components following initial drafting. The authors listed also contributed to the development of methodology, eligibility criteria, and data extraction forms. The original search strategy used in this review was developed by members of the Blueprint Translation Research Group at the Ottawa Hospital with the assistance of the librarian Risa Shorr. All authors approved the final protocol.

Protocol Registration: Berjawi, R., Lalu, M. M., Brehaut, J., & Ferguson, D. (2020, September 13). A Systematic Review of Preclinical Systematic Reviews Protocol: Identifying Key Characteristics and Prevalence of Construct Validity. https://doi.org/10.17605/OSF.IO/FTM8K

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Introduction

Construct validity is an important yet often overlooked type of validity in preclinical *in vivo* animal research (Drozd et al., 2018; Sena & Currie, 2019). It has been defined as whether the model measures or test measures reflects the general construct being measured (Cronbach & Meehl, 1955). This definition emanates from the field of psychological research. In biomedical research, it has been defined as the degree to which interpretations from a particular experiment can be extrapolated to the target they are intended to represent (Henderson et al., 2013). Both definitions focus on whether certain measures reflect or mimic the construct being measured. They differ in what they consider may impact the representation of the construct of interest. In the first definition from psychology, construct validity is assessed in accordance to the underlying mechanism or theory of the animal model in comparison to the human condition it is meant to mimic (Geyer, 2002). Whereas, the biomedical adaptation of the original definition includes experimental conditions including units, settings, treatments, and outcomes chosen by the researcher for the experiment and how these factors help mimic the clinical conditions (Henderson et al., 2013).

When interpreting preclinical study results, researchers should consider the degree of construct validity of the animal model and how it emulates the clinical condition it is meant to mimic. This evaluation of construct validity might help reduce misinterpretations of preclinical study results, which may improve overall preclinical to clinical translation (Trochim, 2007). Construct validity should also be accounted for by researchers in the design and planning of an experiment to ensure the model, outcome measures, and experimental conditions represent the human condition being studied. Despite its importance, it is unclear whether construct validity is being addressed or evaluated in preclinical experiments. Along with others, we assert that

researchers need to justify their choice of measures such as the disease model and outcomes to help assess construct validity (Sena & Currie, 2019).

In order to get a better understanding of the awareness and use of construct validity, we need an indication of how construct validity is being reported and how it is assessed in preclinical studies. Since systematic reviews typically assess the quality of the studies included in the reviews, it was important for to identify whether or not researchers assessed construct validity in systematic reviews, and if so, how was it assessed. An overview is a review that utilizes systematic methods to identify and synthesize the evidence from systematic reviews as their primary unit of analysis (Higgins & Green, 2008; Hunt et al., 2018). Therefore, our objective is to perform an overview of systematic reviews to measure the prevalence of preclinical systematic reviews that mention and assess construct validity and identify how researchers are assessing construct validity.

Objectives

Our three objectives are: (I) To determine the **prevalence of construct validity** reports in preclinical *in vivo* systematic reviews; (II) To determine **the prevalence of construct validity assessment** in preclinical *in vivo* systematic reviews; (III) Synthesize **how construct validity** is evaluated within *in vivo* preclinical systematic reviews of health interventions.

Methods

Eligibility Criteria

The studies of interest for this overview will be preclinical systematic reviews of *in vivo* animal studies pertaining to a human health disease or condition. Included systematic reviews

can focus on any type of health intervention. The included systematic reviews need to mention construct validity. Exclusion criteria include *in vitro* or *ex vivo* systematic reviews, invertebrate animal models, conference abstracts, narrative reviews that do not meet the systematic review criteria stated below, and systematic reviews published as grey literature material.

Eligible systematic reviews must meet three of the following four criteria to be considered a systematic review: (1) Clearly stated set of objectives with explicit methodology; (2) Includes a systematic search; (3) Includes an assessment of validity of findings (e.g., risk of bias assessment); (4) Systematic presentation, synthesis of characteristics and findings of the included studies (Moher, Liberati, Tetzlaff, & Altman, 2009).

Information Sources and Search Strategy

The initial search and identification of systematic reviews was completed as part of another study (Hunniford et al., 2020). A search strategy was created in collaboration with an information specialist and a clinical expert in the field. The literature strategy was developed using keywords related to preclinical *in vivo* health intervention studies. The search was conducted using online databases MEDLINE, Embase, and TOXLINE. Key search terms included systematic review, meta-analysis, preclinical, animal experiment, and *in vivo*. Full-text reviews only in English were considered and the search will be restricted to the past three years (2015- 2018) to ascertain a contemporary view of whether construct validity is being used and evaluated.

Data Management and Study Selection

The literature search completed as part of the study mentioned previously identified a total of 446 systematic reviews after screening by two independent reviewers. The 446 systematic reviews will be uploaded onto Distiller Systematic Review (DistillerSR), an online cloud-based software for reference screening and data extraction.

Data Collection Process

Data will be collected using standardized extraction forms. Data extraction forms will be integrated onto an online abstraction tool using DistillerSR. Data extraction will be performed by two independent reviewers and disagreements resolved by discussion between reviewers or by a third-party member to reach agreement.

Data Items

Data to be extracted from the systematic reviews will include study characteristics (author, year of publication, journal, disease domain, animal species, interventions evaluated). When provided, we will extract the definition of construct validity provided and classify whether it is an original definition or modified from a cited definition. We will also extract any citation provided for definitions of construct validity. Other items include how frequently construct validity was defined and the elements/ items in the definition. Lastly, we will identify construct validity assessments and what instruments, or criteria were used to assess the concept.

Outcomes

One outcome of interest is to measure the prevalence of construct validity mentions in preclinical *in vivo* animal systematic reviews. A mention is simply using the term construct validity in any part of the paper. We will also measure the prevalence of construct validity

assessments in preclinical *in vivo* animal systematic reviews, assessments will include researchers stating that they assessed construct validity in their methods or reporting results of a construct validity assessment. The third outcome of interest is how authors evaluate construct validity within their systematic review including items, questions, or instruments.

Data Synthesis

The prevalence of construct validity mentions, and assessment will be reported as proportions with 95% confidence intervals (CI). Prevalence will be measured by the number of systematic reviews mentioning construct validity per the total number of systematic review articles and similarly for the prevalence of systematic reviews that assess construct validity. We will also evaluate the prevalence in important subgroups of interest including health/disease domain (i.e., cardiovascular, neurobiology, oncology), country of corresponding author, year of publication, and by animal species. To categorize the health domains of the systematic reviews, we will use International Statistical Classification of Disease (ICD)-10. Of the articles that mention construct validity, we will check if it is defined in the article and identify if the definition matches one of the two definitions stated previous (Cronbach & Meehl, 1955; Henderson et al., 2013). We will calculate the number of articles that defined construct validity and of those, the articles that cited either of the two a priori definitions. How authors assessed construct validity, will be evaluated by categorizing as either using an instrument/tool, or criteria (at least one items). Assessment instrument/tool will be classified as a checklist or tool that was established either for the study or commonly used for that specific construct being researched. We will also synthesize the type of instrument/tool. Using these categories, frequencies and 95% CIs will be used to report how researchers are assessing construct validity.

Reporting and Dissemination

The final reporting of this overview of systematic reviews will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The results of the overview will be summarized into a manuscript to be submitted for publication in a peer-reviewed journal.

Funding: None.

Competing Interests: None.

Chapter 4 References

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Chapter 5. An Overview of Preclinical Systematic Reviews: Identifying Key Characteristics and Prevalence of Construct Validity

Preface:

This chapter includes the final manuscript and results for the overview of systematic reviews. The initial manuscript was drafted by Rania Berjawi and co-authors Drs. Fergusson, Lalu, and Brehaut provided revisions and feedback. Visualizations were created and statistical analysis were performed by Rania Berjawi and Drs. Fergusson, Lalu, and Brehaut provided supervision throughout. All authors have reviewed and approved this manuscript. This manuscript has not been submitted for publication yet.

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Abstract

Background: The extent of awareness and understanding of construct validity in preclinical *in vivo* systematic reviews remains unclear. We suggest that construct validity is an important concept that helps research improve the ability to translate research findings from bench to bedside.

Objective: The objective of our study is to perform an overview of systematic reviews to measure the prevalence of preclinical systematic reviews that mention and/or assess construct validity.

Methods: MEDLINE, Embase, and TOXLINE were searched for preclinical *in vivo* systematic reviews evaluating any health intervention between 2015 and 2018. The identified systematic reviews were searched for any mention of construct validity. The outcomes of the systematic review were the prevalence of any construct validity mention and any form of assessment. If construct validity was assessed, we were interested in the details of how it was assessed.

Results: A total of 444 preclinical systematic reviews were identified. Seven systematic reviews mentioned construct validity for a prevalence of 1.6% (95% confidence interval: 0.64% - 3.2%). Three studies mentioned construct validity directly (0.68%; 95% CI: 0.14% – 1.96%) and four mentioned construct validity indirectly (0.90%; 95% CI: 0.25% – 2.29%). None of the studies provided any form of assessment for construct validity.

Conclusion: In conclusion, awareness around construct validity and discussion of this concept in preclinical *in vivo* systematic reviews was limited and any formal assessment was non-existent. We did not identify any tools or criteria to assess construct validity. Our results suggest there needs to be greater discussion around construct validity to enable researchers to understand and appreciate its importance in designing, executing, and interpreting preclinical studies.

Introduction

Construct validity is an important yet often overlooked type of validity in preclinical *in vivo* animal research (Drozd et al., 2018; Sena & Currie, 2019). It has been defined as whether the model or test measures reflects the general construct being measured (Cronbach & Meehl, 1955). This definition emanates from the field of psychological research. In biomedical research, it has been defined as the degree to which interpretations from a particular experiment can be extrapolated to the target they are intended to represent (Henderson et al., 2013). Both definitions focus on whether certain measures reflect or mimic the construct being measured. They differ in what they consider may impact the representation of the construct of interest. In the first definition from psychology, construct validity is affected by the underlying mechanism of the animal model in comparison to the human condition it is meant to mimic (Geyer, 2002). Whereas, the biomedical adaptation of the original definition includes experimental conditions including units, settings, treatments, and outcomes chosen by the researcher for the experiment and how these factors help mimic the clinical conditions (Henderson et al., 2013).

When interpreting preclinical study results, researchers should consider the degree of construct validity of the animal model and how it emulates the clinical condition it is meant to mimic. This evaluation of construct validity might help reduce misinterpretations of preclinical study results thus improving overall preclinical to clinical translation (Trochim, 2007). Construct validity should also be accounted for by researchers in the design and planning of an experiment to ensure the model, outcome measures, and experimental conditions represent the human condition being studied. Despite its importance, it is unclear whether construct validity is being addressed or evaluated in preclinical experiments. Along with others, we assert that researchers

need to justify their choice of measures such as the disease model and outcomes to help assess construct validity (Sena & Currie, 2019).

In order to get a better understanding of the awareness and use of construct validity, we need an indication of when and how construct validity is being reported and, if undertaken, how it is assessed it in preclinical studies. An overview is a review that utilizes systematic methods to identify and synthesize the evidence from systematic reviews as their primary unit of analysis (Higgins & Green, 2008; Hunt et al., 2018). Therefore, our objective is to perform an overview of systematic reviews to measure the prevalence of preclinical systematic reviews that mention and assess construct validity and identify how researchers are assessing construct validity. More specifically, we wanted to determine the prevalence of construct validity mentioned in preclinical *in vivo* systematic reviews; to determine the prevalence of construct validity assessment in preclinical *in vivo* systematic reviews; and to synthesize how construct validity is evaluated within *in vivo* preclinical systematic reviews of health interventions.

Methods

Protocol Registration

The protocol for this overview of systematic reviews was registered on Open Science Framework (https://doi.org/10.17605/OSF.IO/FTM8K). The manuscript is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009).

Eligibility Criteria

The population of interest for this overview was preclinical published systematic reviews of *in vivo* animal studies pertaining to a human health disease or condition. Included systematic reviews could focus on any type of health intervention. Exclusion criteria included *in vitro* or *ex*

vivo studies, invertebrate animal models, conference abstracts, narrative reviews that do not meet the systematic review criteria stated below, and systematic reviews published as grey literature material.

Eligible studies had to meet three of the following four criteria to be considered a systematic review: (1) Clearly stated set of objectives with explicit methodology; (2) Included a systematic search; (3) Included an assessment of validity of findings (e.g. risk of bias assessment); (4) Systematic presentation, synthesis of characteristics and findings of the included studies (Moher et al., 2009).

Information Sources and Search Strategy

The initial search and identification of systematic reviews was completed as part of another study (Hunniford et al., 2020). The search strategies were created in collaboration with an information specialist and a clinical expert in the field. The literature strategies were developed using keywords related to preclinical *in vivo* health intervention studies. The searches were conducted using online databases MEDLINE, Embase, and TOXLINE. Key search terms included systematic review, meta-analysis, preclinical, animal experiment, and *in vivo*. Full-text articles in English were considered and the search was restricted to three years (2015-2018) to reflect a contemporary view of whether construct validity was being integrated and evaluated.

Data Management and Study Selection

The results from literature search were uploaded onto Distiller Systematic Review (DistillerSR), an online cloud-based software for reference screening and data extraction. Two independent reviewers screened the references for relevance based off of the inclusion and exclusion criteria.

Data Collection Process

Data was collected using standardized extraction forms. Data extraction forms were integrated onto an online abstraction tool using DistillerSR. Data extraction for individual studies was completed by two reviewers from the previous study. Further data extraction for papers mentioning construct validity was performed by one reviewer.

Data Items

Data extracted from the included systematic reviews included study characteristics (author, year of publication, journal, disease domain, animal species, and interventions evaluated). When provided, we extracted the definition of construct validity provided and classified whether it is an original definition or modified from a cited definition. We also extracted any citation provided for definitions of construct validity. Other items included how frequently construct validity was defined and the elements/ items as part of the definition. Lastly, we identified construct validity assessments and what instruments, or criteria were used to assess.

Outcomes

One of our main outcomes of interest was the prevalence of any mention of construct validity within the preclinical *in vivo* animal systematic reviews. A mention was simply using the term construct validity in any part of the paper. We also measured the prevalence of construct validity assessments in preclinical *in vivo* animal systematic reviews, assessments included researchers stating that they assessed construct validity in their methods or the reporting of results of a construct validity assessment. The third outcome was how authors evaluate construct validity within their systematic review including items, questions, or instruments.

Data Synthesis

The prevalence of construct validity mentions, and assessment were reported as proportions with 95% confidence intervals (CI) using the Clopper-Pearson Exact method. Prevalence was measured by the number of systematic reviews mentioning construct validity per the total number of systematic review articles and similarly for the prevalence of systematic reviews that assess construct validity. We also evaluated the prevalence of construct validity mentions in important subgroups of interest including health/disease domain (i.e., cardiovascular, neurobiology, oncology), country of corresponding author, year of publication, and by animal species. We used the International Statistical Classification of Disease (ICD)-10 to categorize the health domains of the systematic reviews. Of the articles that mentioned construct validity, we evaluated whether construct validity was defined and, if so, whether it matched one of the definitions (Cronbach & Meehl, 1955; Henderson et al., 2013). We calculated the proportion and 95% CI of articles that defined construct validity and of those, the articles that cited either of the two a priori definitions. How authors assessed construct validity, was evaluated by categorizing as either using an instrument/tool, or criteria (at least one items). Assessment instrument/tool will be classified as a checklist or tool that was established either for the study or commonly used for that specific construct being researched. We synthesize the type of instrument/tool. Using these categories, frequencies and 95% CIs were used to report how researchers assessed construct validity.

Results

The literature search yielded 2356 references of which 444 were identified as systematic reviews published between 2015 to 2018. A total of seven systematic reviews mentioned construct validity within the article with a prevalence of 1.6% (95% confidence interval: 0.64% - 3.2%) (Figure 1). Study characteristics of the seven studies that mentioned construct validity are

summarized in Table 1. Five out of the seven systematic reviews were evaluating pharmacological interventions and the other two evaluated a gene therapy intervention. Five of the systematic reviews with construct validity used rodents, mainly mice, whereas one was on Rhesus Macaques, and another was not specified. Nervous system disorders were the most common medical classification evaluated in the systematic reviews (n=3; 0.68%; 95% CI: 0.14% - 1.96).

Three studies mentioned construct validity directly by using the term construct validity (0.68%; 95% CI: 0.14% – 1.96%) and four mentioned construct validity indirectly by referring to the concept without using the term (0.90%; 95% CI: 0.25% – 2.29%). Construct validity was primarily mentioned in the introduction of the systematic review (n=4). None of the systematic reviews provided a definition or cited a paper referencing a definition for construct validity. None of the systematic reviews assessed construct validity in any form. Two of the studies assessed other forms of validity including internal, external, predictive, and face validity (Kristensen, Nierenberg, & Østergaard, 2018; Sadigh-Eteghad et al., 2017).

Discussion

The aim of this overview of systematic reviews was to evaluate how often researchers discuss and assess construct validity in the conduct and reporting of systematic reviews. Our results demonstrate the lack of awareness and integration of construct validity discussion in preclinical *in vivo* systematic reviews. Furthermore, no systematic review assessed construct validity, suggesting an absence of tools available for researchers to use to assess construct validity. This may be related to poor awareness of the importance of construct validity among researcher, funders, and journals.

Our findings indicate the necessity of increasing awareness of construct validity in order for it to be better understood and integrated into knowledge synthesis methods in a similar manner to common risk of bias assessments for internal and external validity. Increased awareness can enable the research community to further discuss and debate about construct validity more effectively and in turn create tools to help assess it.

Though construct validity was not explicitly defined in any of the systematic reviews, three studies mentioned key elements when referring to construct validity. Two elements raised were 1) that construct validity should include the mechanism of disease of the model and how it relates to the human condition; and 2) construct validity should consider the severity of the model and what stage of the clinical disease does it match. The first element referring to the mechanism of the animal model can be linked to the Cronbach and Meehl definition of construct validity, where the mechanism of disease in the preclinical model was achieved by altering gene and this gene alteration should be the same one that is impacted in the clinical condition (Kristensen et al., 2018). Kristensen et al. (2018), discussed construct validity directly, stating that the gene association between the mouse model and the human condition, bipolar disorder, constitutes construct validity. The paper did not elaborate further on construct validity directly, however, there were sections dedicated to face and predicative validity of the mouse model used in the studies using various criteria. The second element identified in the systematic reviews discusses the severity of the animal model falls more appropriately under the Henderson et al. definition. An animal model can represent the same disease, such as liver disease, however, acute and chronic stages of this disease are pathologically different therefore if a model does not reflect the stage of disease of interest it can impact how the results can be translated to the clinical condition (Wang et al., 2015).

The purpose of systematic reviews is to assess a topic in depth, in a rigorous and methodical manner (Jones & Evans, 2000). Therefore, assessing potential sources of bias such as items of construct validity should be included in the systematic review process of preclinical *in vivo* studies to adequately assess these studies. Likewise, preclinical research studies should report the construct validity of their experiment and discuss how it was taken into account in the design and planning of the study. This may enable systematic reviewers to categorize the degree to which various animal models, outcomes, and settings replicate the human condition of interest. Consequences of not considering construct validity can lead researchers to make inaccurate generalizations of the study results. If a model fails to recapitulate the human condition then evidence suggests that it may lead to failed clinical translation (Hirst et al., 2014).

A limitation to this study is that we restricted our search to systematic reviews from 2015 to 2018. We did this to capture a contemporary view of how construct validity is being discussed in systematic reviews, however, looking at systematic reviews from previous years we may have been able to identify more studies that mentioned construct validity. We may have also been able to identify a time trend of construct validity discussion in systematic reviews. Another limitation was that we had not performed a risk of bias analysis because our goal was to identify the prevalence of systematic reviews discussing construct and if they assessed it. However, it may have been useful to look at the relationship or trend between the risk of bias of the studies and whether they discussed or evaluated construct. A risk of bias assessment tool that could have been used for this overview is *A MeaSurement Tool to Assess systematic Reviews-2* (AMSTAR-2).

Conclusion

Our overview of systematic reviews highlights the lack of attention to and assessment of construct validity in the conduct of preclinical *in vivo* systematic reviews. Clearly, greater awareness and discussion on the importance and definition of construct validity is needed within the research community, so that researchers can begin to consider assessing construct validity in preclinical systematic reviews.

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Appendix A - Tables

Table 1. Study Characteristics of Studies Mentioning Construct Validity

Author (Year)	Journal	Intervention evaluated	Disease medical classification (ICD-10)	Animal species
Sadigh-Eteghad (2017)	PLOS One	Pharmacological	Nervous System Disorders	Rodents
Ianara (2017)	Phytotherapy Research	Pharmacological	Nervous System Disorders	Not specified
Wang (2015)	Expert Review of Gastroenterology & Hepatology	Pharmacological	Diseases of the digestive system	Mice
MacVittie (2015)	Health Physics	Pharmacological	Diseases of the genitourinary system	Rhesus Macaques
Foley (2015)	Journal of Alzheimer's Disease	Gene Therapy	Nervous System Disorders	Mice
Kristensen (2018)	Molecular Psychiatry	Gene Therapy	Mental and behavioural disorders	Mice
Federspiel (2018)	Ophthalmic Genetics	Pharmacological	Diseases of the eye and adnexa	Mice

Table 2. Construct Validity Characteristics

Author (Year)	CV mentioned directly or indirectly	Section CV was mentioned?	Did they define CV?	What are key elements/items in the definition?	Did the paper assess CV?	Were other forms of validity assessed? (type)
Sadigh-Eteghad (2017)	Directly	Introduction	No	NR	No	Yes (internal and external validity)
Ianara (2017)	Indirectly	Introduction	No	NR	No	No
Wang (2015)	Indirectly	Introduction	No	Severity of animal model resembling different stages of human condition	No	No
MacVittie (2015)	Directly	Conclusion	No	NR	No	No
Foley (2015)	Indirectly	Methods	No	Genes and mechanism involved in animal model and comparison to human conditions	No	No
Kristensen (2018)	Directly	Introduction	No	Gene association in animal and human condition	No	Yes (face and predictive validity)
Federspiel (2018)	Indirectly	Results	No	NR	No	No

Appendix B – Figures

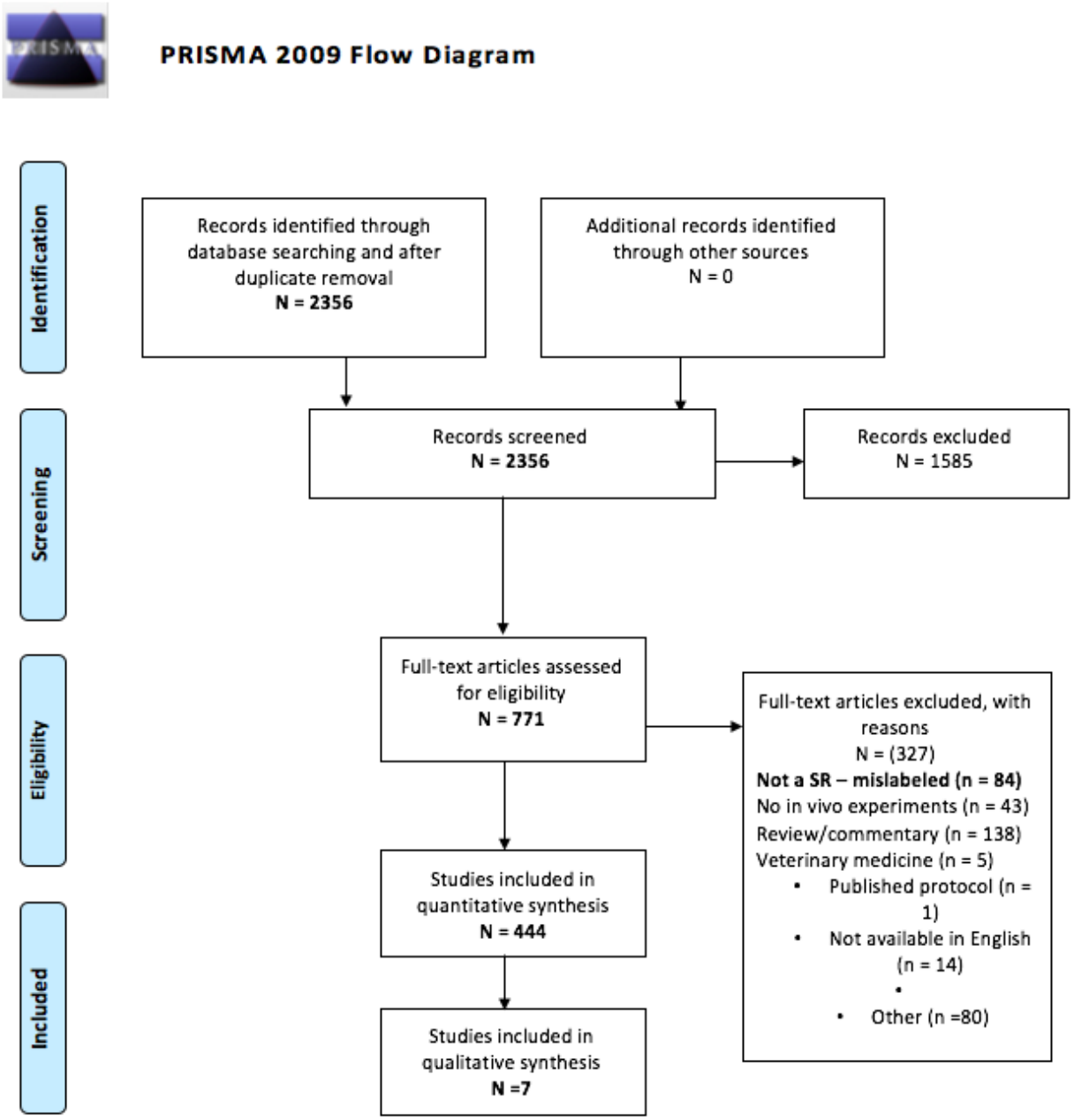

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) diagram.

Appendix C – Search Strategy

Database: Embase Classic+Embase <1947 to 2019 March 20>, Ovid MEDLINE(R) ALL <1946 to March 20, 2019>
Search Strategy:
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1 meta-analysis.pt. (98487)
2 (meta-analy* or metaanaly* or metanaly* or met analy*).ti,ab. (333373)
3 "meta-analysis as topic"/ (42912)
4 or/1-3 (378559)
5 review.pt,ab. (6228648)
6 systematic.tw. (694670)
7 5 and 6 (349992)
8 (systematic* adj5 (review* or overview*)).ti,ab. (342285)
9 4 or 7 or 8 (636452)
10 (comment or editorial or letter).pt. (3351144)
11 9 not 10 (617380)
12 limit 11 to animals (17717)
13 exp Animal Experimentation/ (2357279)
14 exp models, animal/ (1764737)
15 experiment*.ti,ab. (4181761)
16 limit 15 to animals (1617517)
17 13 or 14 or 16 (4251842)
18 11 and 17 (7489)
19 12 or 18 (20277)
20 meta-analysis.pt. (98487)
21 (meta-analy* or metaanaly* or metanaly* or met analy*).tw,kw. (337365)
22 "meta-analysis as topic"/ (42912)
23 or/20-22 (382185)
24 review.pt,ab. (6228648)
25 systematic.tw,kw. (697610)
26 24 and 25 (351511)
27 (systematic* adj5 (review* or overview*)).ti,ab. (342285)
28 23 or 26 or 27 (639738)
29 (comment or editorial or letter).pt. (3351144)
30 28 not 29 (620334)
31 limit 30 to animals (17844)
32 exp Animal Experimentation/ (2357279)
33 exp models, animal/ (1764737)
34 experiment*.tw,kw. (4303640)
35 limit 34 to animals (1672077)
36 32 or 33 or 35 (4300654)
37 30 and 36 (7555)
38 31 or 37 (20419)
39 limit 38 to yr="2018" (1895)

40 (2018* not (2018010* or 2018011* or "20180120" or "20180121")).dt. (1206782)
41 38 and 40 (749)
42 39 or 41 (1961)
43 42 use medall (1085)
44 exp "animal experiment"/ or (animal* and stud*).tw. or exp "animal model"/ or (animal* and model*).tw. (4142400)
45 environmental exposure.tw. (14612)
46 exp environmental exposure/ (380665)
47 exp toxicology/ (100105)
48 toxicology.tw. (62210)
49 exp genetic toxicology/ (970)
50 exp comparative toxicology/ (260)
51 mutagen*.tw. (235710)
52 exp mutagenic agent/ (18732)
53 carcinogen.tw. (50195)
54 exp carcinogen/ (145604)
55 drug toxicity.fs. (537731)
56 adverse drug reaction.fs. (1260505)
57 side effect.fs. (848786)
58 or/45-57 (2586499)
59 44 and 58 (299226)
60 (meta and analy*).tw. (339980)
61 meta analysis/ (256415)
62 (systematic* and review*).tw. (403251)
63 "systematic review"/ (299056)
64 or/60-63 (697228)
65 59 and 64 (2030)
66 (2018* not (2018010* or 2018011* or "20180120" or "20180121")).dc. (1613924)
67 65 and 66 (135)
68 67 use emczd (135)
69 43 or 68 (1220)
70 remove duplicates from 69 (1190)
71 70 use medall (1085)
72 70 use emczd (105)

Appendix D – PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Pg. 169
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Pg. 171
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pg. 172 – 173
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pg. 173
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Pg. 173
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pg. 173 - 174
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pg. 174
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Pg. 174; Appendix C (Pg. 186 – 187)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pg. 174
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pg. 175
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Pg. 175
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Pg. 175
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Pg. 176
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pg. 176
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pg. 176 – 177
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Pg. 177
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pg. 177 – 179
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pg. 179
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pg. 180
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Pg. 180

Chapter 6. Final Discussion and Summary

Summary of Findings

The thesis was composed of both a scoping review and an overview of systematic reviews, which evaluated the literature for construct validity in relation to preclinical *in vivo* animal studies. The scoping review aimed to evaluate the published literature on construct validity in preclinical *in vivo* research and map out how construct validity is being defined and, through content analysis, how it is characterized. The overview of systematic reviews focused on how prevalent the concept of construct validity was present in published *in vivo* systematic reviews in terms of its citation, whether it was formally evaluated, and if it was evaluated, how it was measured.

The scoping review highlighted the very little attention construct validity receives in the *in vivo* literature. Though the limited discussion around construct validity has been increasing over time, there was a paucity of articles that mentioned or discussed construct validity outside of mental and behavioural disorders. A content analysis was performed in the scoping review to organize the definitions of construct validity provided by researchers into meaningful categories. We then determine the frequencies each category. The six categories generated from the construct validity definitions extracted from the included studies were: choice of model supported by known theory; choice of model supported by known mechanism; choice of model needs to match the human condition; choice of outcome measure needs to match the human condition; experimental conditions need to represent the human condition; and the model measures what it reports to. The most frequent category to define construct validity was “choice of the model supported by known mechanism”.

There were separate purposes for conducting the scoping review and the overview. The scoping review showed us how construct validity was being defined and leading into the overview we wanted to see if and how researchers were assessing construct validity, and the prevalence at which it was being reported. The scoping review had identified 6 categories through the content analysis that were used to identify whether researchers were discussing construct validity indirectly in the overview. These six categories also provided a set of characteristics that were available to use in the overview to see if researchers chose to assess construct validity.

In our overview of systematic reviews, we found that very few systematic reviews of preclinical *in vivo* studies mentioned, discussed, or evaluated construct validity. Importantly, none of the systematic reviews that mentioned construct validity provided a definition for construct validity. Furthermore, we found that none of the systematic reviews assessed construct validity in any form. Both the scoping review and overview reinforced the idea that construct validity awareness and discussion is scarce and not receiving sufficient attention in preclinical research.

Thesis Implications

This thesis demonstrated that construct validity is a poorly understood concept in preclinical research as a variety of definitions and key elements were presented and cited. It is critical to understand construct validity is vital to establishing whether a model is translatable, applicable, and relevant to the clinical setting it is trying to represent. Understanding which factors, behaviour, or mechanism the animal model is targeting may better inform and help researchers translate the results of the experiment to the proper subgroups of the human population it is trying to represent (Zike et al., 2017). Along with internal and external validity,

awareness of construct validity is necessary to judge the strengths and weaknesses of possible animal models during the planning and design of experiments (Yang & Gray, 2011). It is important for researchers to evaluate construct validity, as poor construct validity may be harmful to the scientific validity and reproducibility of outcomes published and compromise the outcome of the study (Würbel, 2017).

Our scoping review found there is no clear uniform and well-accepted definition of construct validity. Moreover, this increase is heavily focused in the mental and behavioural medical conditions leaving gaps in awareness and discussion in other biomedical areas of research. Our findings from our overview of systematic reviews demonstrated that assessment of construct validity and its impact on findings is non-existent. This finding may be due to the lack of a uniform definition, or a lack of understanding and awareness of the importance of construct validity as demonstrated in our scoping review.

The idea of how an *in vivo* experimental model is likely to translate/ transfer to the clinical model of disease is likely front and centre with researchers as they design their experiments, yet such discussions, deliberations and choices are not explicitly reported in their publications. The primary goal of this thesis was to advance discussion and debate about the concept of construct validity and its importance in preclinical research. Doing so will help produce a uniform and acceptable definition and the development of tools to evaluate.

There may be a link between studies with good construct validity and an increased chance of reproducibility and replicability by other researchers. Poor construct validity may be harmful to the scientific validity and reproducibility of outcomes published by compromising the outcome of the study. If a study is performed trying to minimize factors that can impact construct validity negatively then it is likely that the research will have a higher chance being replicated

and reproduced by other researchers. Future studies should look at the impact of construct validity of studies and how it relates to reproducibility or replication. Researchers need to find a way to quantify the relationship between construct validity and reproducibility and replicability. Future studies should look at the impact of construct validity of studies and how it relates to reproducibility or replication into clinical settings.

Future research should also aim to develop a uniform definition of construct validity. This will help enable researchers to create and validate tools and/or important criteria needed to assess construct validity in preclinical research. Such tools and criteria can help evaluate the impact of construct validity within and between studies. The overall goal is to understand construct validity and have the proper guidance to improve the translatability of experimental results.

Chapter 6 References

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