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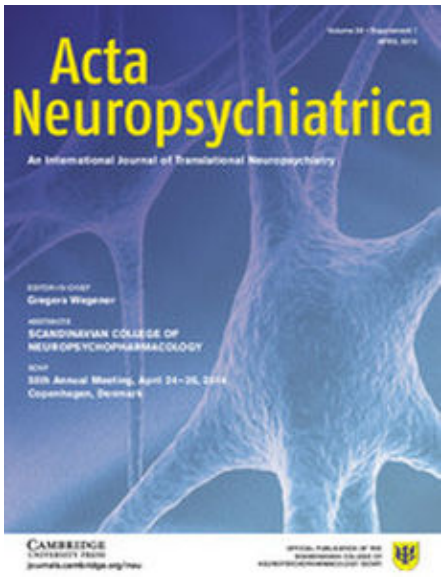

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ABSTRACTS

1st AUGUST CONFERENCE

AARHUS UNIVERSITY GROUP FOR UNDERSTANDING SYSTEMATIC REVIEWS AND METAANALYSES IN TRANSLATIONAL PRECLINICAL SCIENCE

November 17th 2015
Aarhus, Denmark

AARHUS UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

Danmarks 3R-Center
RRR
Replacement Reduction Refinement

Collaborative Approach to Meta Analysis and
·C·A·M·A·R·A·D·E·S·
Review of Animal Data from Experimental Studies

SYRCLE

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LECTURE

Systematic review and meta-analysis of data from non-human in vivo research: Past, present and future.

Malcolm Macleod,

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The first systematic review of data from non-human in vivo research was published in 1979, and the first meta-analysis was published in 1989, but it is only in the last 12 years that these approaches have seen widespread application. The first CAMARADES review (of nicotinamide in experimental stroke) was published in 2004, and since that time the Edinburgh group have published a further 42 systematic reviews and 2 methodology papers.

While CAMARADES (the collaborative approach to meta-analysis and review of animal data from experimental studies) was initially a collaboration between Howells in Melbourne and Macleod in Edinburgh, it has since evolved to be a global umbrella organisation supporting scientists conducting such reviews, with coordinating centres in Edinburgh, Hobart, Nijmegen and Ottawa.

The wider collaboration now considers animal models not just of stroke but includes also multiple sclerosis, Alzheimer's disease, Parkinson's disease, depression, psychosis, pain, traumatic brain injury, epilepsy, infection, neonatology and myocardial ischaemia.

A recent consensus meeting identified priority areas for methodological development including reporting standards for systematic reviews of animal studies; Data and text mining and machine learning as tools to accelerate systematic reviews; Protocols and protocol registry; application of the GRADE approach to in vivo research; Publication bias and its assessment; Network Meta-analysis; and use of Multivariable meta-regression.

In addition to these areas, there is large untapped potential in using SRMA to enhance our understanding of pathophysiological processes in animal models; to improve modelling by optimising sample size; to understand the different relevance of different outcome measures in animal models; and to provide assessments of reporting of risks of bias to inform institutional improvement activities.

Maturation of the field is evident from the rich range of current activities, from the launch of the dedicated journal "Evidence Based Preclinical Medicine", and from increasing rates of funding success.

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LECTURE

Improving animal based research - From 3Rs to SRs

Judith van Luijk

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The research group of the Central Animal Facility at the Radboudumc focus on improving animal-based research. In the last decade the focus of this group has gradually shifted from 3R-research (Replacement, Reduction and Refinement) towards systematic reviews of animal studies.

During this presentation I will elaborate on the research performed by the 3R Research Centre (later SYRCLE) in the research programme "Animal research limited". These findings formed the basis for the follow-up programme "More knowledge with fewer animals". This research programme funded by the Dutch government, stimulates a number of initiatives to improve quality and transparency of animal-based research.

I will also give a brief introduction of the various activities SYRCLE has undertaken to facilitate the process of systematic reviews of animal studies, including the development of methodology, guidelines and training programs.Systematic review and meta-analysis of data from non-human in vivo research: Past, present and future.

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LECTURE

Systematic reviews: principles, methods and reporting standards.

Hanna Vesterinen

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Systematic reviews provide a useful summary of available evidence on any research topic and are increasingly being used to make important clinical and health-related decisions. I will discuss three specific topics related to

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systematic reviews: their principles, methods and reporting standards. In the first section, I will explain that systematic reviews are scientific studies and must be conducted, reported and evaluated with the same rigour that we expect from any other scientific study. In the section on methodology I will discuss the importance of the protocol and some practical issues relating to assessing study quality. I will also focus on explaining the background to understanding and performing a meta-analysis and exploring heterogeneity. Specifically I will discuss the principle of the "true" population effect size and how this defines our exploration of heterogeneity and the appropriate methods used for meta-analysis. In the third section I will discuss reporting standards with a focus on the current state of reporting and quality, why guidelines are necessary and how they will improve the future of systematic review conduct and reporting.

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LECTURE

Ease the process of conducting Systematic Reviews of animal studies

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www.syrcle.nl

Methodology of systematic reviews (SR) of preclinical intervention studies is largely comparable to systematic reviews of Randomized clinical trials (RCT). There are however some differences between RCTs and animal intervention studies, and as a consequence the SR methodology used for summarizing evidence of clinical trials needs to be adapted to conduct SRs of preclinical animal intervention studies.

In this presentation tools to facilitate the conduct and interpretation of systematic reviews of animal studies are discussed. Tools that are discussed focus on the searching process (1-3), the risk of bias analysis (4) and statistically combining studies (5, 6). Recently SYRCLE also published a protocol for systematic reviews of animal studies (7). In such a protocol the methodology for a SR can be pre specified in order to reduce the risk on reporting bias. Moreover, a tool to grade the quality of evidence resulting from animal studies and improve the interpretation and translation of animal studies is being developed.

In summary, SRs of animal studies are urgently needed to identify knowledge gaps, to reduce unnecessary duplication of animal studies and to choose animal models based on evidence. In addition, they are useful to identify factors influencing treatment efficacy and safety (exploring efficacy and safety of treatments) and guide clinical trials. Several tools to ease the process of SRs of animal studies have already been developed but more are needed and will be developed.

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LECTURE

Protocol registration and PROSPERO

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Systematic reviews usually provide the evidence base upon which health and social care decisions are made so they should be robust and free from bias. Health research resources are finite so unnecessary duplication should be avoided. Concern about, and evidence of biases associated with systematic reviews highlighted the absence of any facility outside organisations such as the Cochrane and Campbell Collaborations, to register a review protocol. This led to the development of PROSPERO.

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PROSPERO is the open access prospective register for systematic review protocols launched by the Centre for Reviews and Dissemination in February 2011. The key aims of the register are to facilitate transparency in the review process by prospectively recording planned methods and to provide a searchable database of ongoing reviews that will assist in the avoidance of unplanned duplication of work.

Researchers enter a minimum 22 item dataset that takes on average 30 minutes to complete; submissions are checked against the inclusion criteria and for sense, but are not peer reviewed, before being published on the register.

Records are permanent and registrants are encouraged to add protocol amendments and finally, links to their published review. Records are reactivated when a review is being updated, making the history available all in one place. All changes are recorded in an audit trail within the free access public platform.

PROSPERO is now well established and contains over 10,000 records. From the initial focus on reviews of interventions, the scope for inclusion has been widened to take in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome. In response to approaches from CAMARADES and SRYCLE, and the growing interest in, and need for systematic reviews of preclinical studies, plans for the inclusion of protocols for systematic reviews of preclinical studies are well underway.

This initiative is a major step towards achieving the aim of expanding the scope of PROSPERO to ultimately include all systematic reviews for which there is a health related outcome in the broadest sense. By including preclinical and clinical review protocols in one register we hope to further promote the importance of evaluating all the evidence that impacts human health, whether it's in the clinical setting or at the bench.

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SYMPOSIUM

S1.1 Persistent changes in animal behaviour after exposure to psychotropic drugs - a systematic review

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Background: Prescriptions for psychotropic drugs are increasing annually, in part because more people are taking these drugs for longer periods of time.. Most studies of psychotropic drugs however, only assess short-term benefits and harms. We assessed whether exposure to psychotropic drugs caused persistent harms in mammals after a follow-up period without drugs.
Methods: We searched PubMed, Biosis and EMBASE, with no date limitations, for controlled preclinical studies. Main inclusion criteria were: animal studies, with no priming of behaviour, with follow-up behavioural assessments after at least 90 days without drugs. Two researchers independently extracted data for animal characteristics, study design and behavioural outcomes of sleep, addiction, aggression, anxiety, depression, locomotion, cognition (with memory and learning) and social behaviour (including sexual behaviour). Data were combined in meta-analyses. Where this was inappropriate, a narrative synthesis was performed.
Results: We included 31 studies in our analysis. Heterogeneity was high (I-square=64-94% for five outcome categories) and no subgroup analysis accounted for this. Risk of bias assessment showed overall lack of blinding, randomisation and some degree of selective reporting. Descriptive analysis showed tendency towards persistent harms in social behaviour and cognition. For the remaining outcomes there was little difference between intervention and control groups.
Conclusions and perspectives: There were weak indications that animals experienced persistent harms from previous exposure to psychotropic drugs. The methodology and experimental design of the summarized research was poor or poorly reported. We strongly recommend authors use ARRIVE guidelines when reporting animal research, thereby increasing the translational value of their work.

S1.2 Tissue engineering of the urethra: a systematic review of preclinical and clinical studies

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Tissue engineering is regarded as a high potential treatment option for urethra reconstruction since current treatments, often being autologous tissue transplants, are hindered by the limited availability of donor tissue and donor site morbidity. Despite its potential and the progress made with in vitro and animal experiments, clinical translation is still imperceptible. By performing a systematic and unbiased meta-analysis of all primary animal and clinical (case) studies, we aim to stimulate the translation of engineered urethra's from bench-to-bedside.
A comprehensive search was performed in Pubmed and EMBASE using urethra, tissue engineering and animal/patient search components. After literature was screened for relevance, study characteristics and data were extracted for included studies. A statistical meta-analysis was performed to investigate the influence of the biomaterial that was used, the addition of (stem)cells and the animal model on the clinical outcome. Functionality, occurrence of side effects and dropouts were used as outcome measures.
The systematic search resulted in the inclusion of 52 animal studies and 19 human studies for the meta-analysis. Preliminary results of the meta-analysis showed a vast increase in positive outcome if cells were added to the grafts before implantation in animal models.
In general, we observed that the quality and the reporting of the conducted animal studies was poor. To increase the efficiency of preclinical studies and thereby facilitating clinical translation, it will be of utmost importance to perform high quality animal experiments according to the same principles as used for clinical experiments.

S1.3 Drug delivery systems for ovarian cancer treatment: a systematic review and meta-analysis of animal studies

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Ovarian cancer treatment involves chemotherapy that has serious limitations, such as rapid clearance, unfavorable biodistribution and severe side effects. To overcome these limitations, drug delivery systems (DDS) have been developed to encapsulate chemotherapeutics for delivery to tumor cells. Here, we assess the efficacy of chemotherapy in DDS on survival and tumor growth inhibition in animal studies.
We searched PubMed and EMBASE (via OvidSP) to identify in vivo studies evaluating chemotherapeutics encapsulated in DDS for ovarian cancer treatment. Studies were assessed for quality and risk of bias. Study characteristics were collected and outcome data (survival or tumor growth inhibition) were extracted and used for meta-analyses. Meta-analysis was performed to identify and explore which characteristics of DDS influenced treatment efficacy.
A total of 44 studies were included after thorough literature. The risk of bias was difficult to assess, mainly because of incomplete reporting. A total of 17 studies (377 animals) and 16 studies (259 animals) could be included in the meta-analysis for survival and tumor growth inhibition, respectively. In the majority of the included studies chemotherapeutics entrapped in a DDS significantly improved efficacy over free chemotherapeutics regarding both survival and tumor growth inhibition. Subgroup analyses, however, revealed that cisplatin entrapped in a DDS did not result in additional tumor growth inhibition compared to free cisplatin, although it did result in improved survival. Micelles did not show a significant tumor growth inhibition compared to free chemotherapeutics, which indicates that micelles may not be a suitable DDS for ovarian cancer treatment. Other subgroup analyses did not identify specific characteristics of DDS that affected treatment efficacy.
This systematic review shows the potential, but also the limitations of chemotherapy by drug delivery systems for ovarian cancer treatment. For future animal research, we emphasize that data need to be reported with ample attention to detailed reporting.

S1.4 Articular Cartilage Regeneration Using Biomaterials Implanted After Microfracturing: A Systematic Review and Meta-Analysis of Animal Studies

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Microfracture surgery is applied in clinical practice to regenerate articular cartilage, but this procedure results only in temporary clinical improvements and mechanically inferior fibrocartilage formation. Regenerative medicine may offer advantages by implantation of biomaterials stimulating guided tissue regeneration.
This systematic review and meta-analysis investigates the efficacy of cartilage regeneration after implantation of biomaterials in osteochondral defects in animal studies, as compared to treatment without biomaterials. Pubmed and EMBASE databases were searched comprehensively using tissue engineering, cartilage and animal-related search terms. Primary studies were included in which microfracturing was performed or osteochondral defects were created in the knee or ankle joint of healthy animals, followed by implantation of biomaterials. Study characteristics were extracted and the methodological quality was assessed. A meta-analysis was performed for studies containing a comparison between implanted biomaterials and a non-treated control group and using semi-quantitative histology as outcome measure.
The literature search resulted in 6688 studies, of which 152 studies were used for quality assessment and meta-analysis. Overall, a significant 16.02% improvement in cartilage regeneration was found for implantation of biomaterials compared to non-treated empty defects. There were no differences in study outcome between animal models, biomaterials from natural or synthetic origin, hydrogels or scaffolds, and between various implanted materials. Incorporation of biologicals improved cartilage regeneration compared to control biomaterials by 8.28%. No differences were found between biomaterials loaded with the growth factors bone morphogenetic protein, fibroblast growth factor, transforming growth factor, and platelet-rich plasma. Quality assessment indicated poor reporting of the experimental design for most studies, impeding assessment of actual risk of bias/overestimation.
The systematic review and meta-analysis provides an overview of all literature available related to implantation of biomaterials after microfracturing in preclinical models. Implantation of acellular biomaterials improved cartilage regeneration compared to microfracturing alone, which was further improved by the additional loading of biologicals.

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This work was supported by a grant from the Dutch government to the Netherlands Institute for Regenerative Medicine
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POSTERS

P1 From animal model to translational strategy

Cathalijn HC Leenaars[1], Ali Molavi[2], Frans R Stafleu[2], Rob BM de Vries[1], Carine Punt[3], Jan-Bas Prins[4], Tineke Coenen[4], T Ritsema[3], Wouter Beumer[3] Merel Ritskes-Hoitinga[1], Franck BL Meijboom[2,5].

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Background: The translational value of animal studies is worryingly low1-3. This might be caused by inter-species differences and / or inadequate methodology of animal studies4,5. We hypothesise that improving translational success requires so-called translational strategies. Important aspects are an integrated approach covering the entire research chain and the patient's perspective.
Methods: These aspects will be adressed in 6 work packages:
WP1: Getting grip on animal models Systematic reviews of animal studies will help choosing the optimal experimental design for the case studies: CF and RA.
WP2: Quality versus translational value A combined meta-analysis of clinical and preclinical data will reveal whether there is a relationship between preclinical study quality and translation.
WP3: Exploring the research chain We will describe the current research chain, explore potential improvements and analyse obstacles to change, based on literature,expert-interviews and stakeholder-meetings.
WP4: Uncertainty as key concept Ethical analyses will address e.g. uncertainty of future outcomes of experiments, the extent of translational power needed to improve trust in research, and the legitimacy to restrict individual freedom to improve the quality of research.
WP5: Building Translational Strategy New models will be developed or existing models will be adapted to fit an integrated translational strategy. We strive to perform an ideal animal study.
WP6: Implementation and valorisation Integration of our results into new or existing guidelines.
Perspectives: Overall, this project (NWO_313-99-310) aims to provide a framework for tackling translation. It runs from SEP-2015 through DEC-2019.

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P2 The modifying effect of anesthetic drugs on metastasis in experimental cancer models

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Background: Distant metastasis or local recurrence after primary tumour resection remain a major clinical problem. The anesthetic technique used during or direct after oncologic surgery is suggested to influence the metastatic process. We analyzed the animal evidence regarding the influence of anesthetic techniques on tumor metastasis, while we await the results of ongoing RCTs in patients

Methods and results: 20 studies met the inclusion criteria. Data on number of metastases could be retrieved from 17 studies. These studies described 41 independent comparisons of which 33 could be included in meta analysis (MA). The incidence of metastases was studied in 3 unique papers. From these 3 papers, data on 7 independent comparisons could be extracted and included in MA. Overall, anaesthetics influence the number and incidence of metastases in experimental cancer models. Local anaesthetics seem to decrease the number of metastases, whereas general anaesthetics, and especially volatile anaesthetics seem to increase the amount and risk on metastases.

Conclusions: On the basis of this review, it appears to be safe to use local anaesthetics during surgery in cancer patients. It might even be beneficial. General anaesthetics, and especially volatile anaesthetics, however, might be harmful. They might increase metastasis and therefore should be used carefully as long as the results of clinical trials confirming this harmful effect are not published. New animal studies are warranted, and should focus on the effects of the most commonly used volatile and local anaesthetics.

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