



Brian Jackson, *Untitled 6* Artwork from Reflections Art in Health

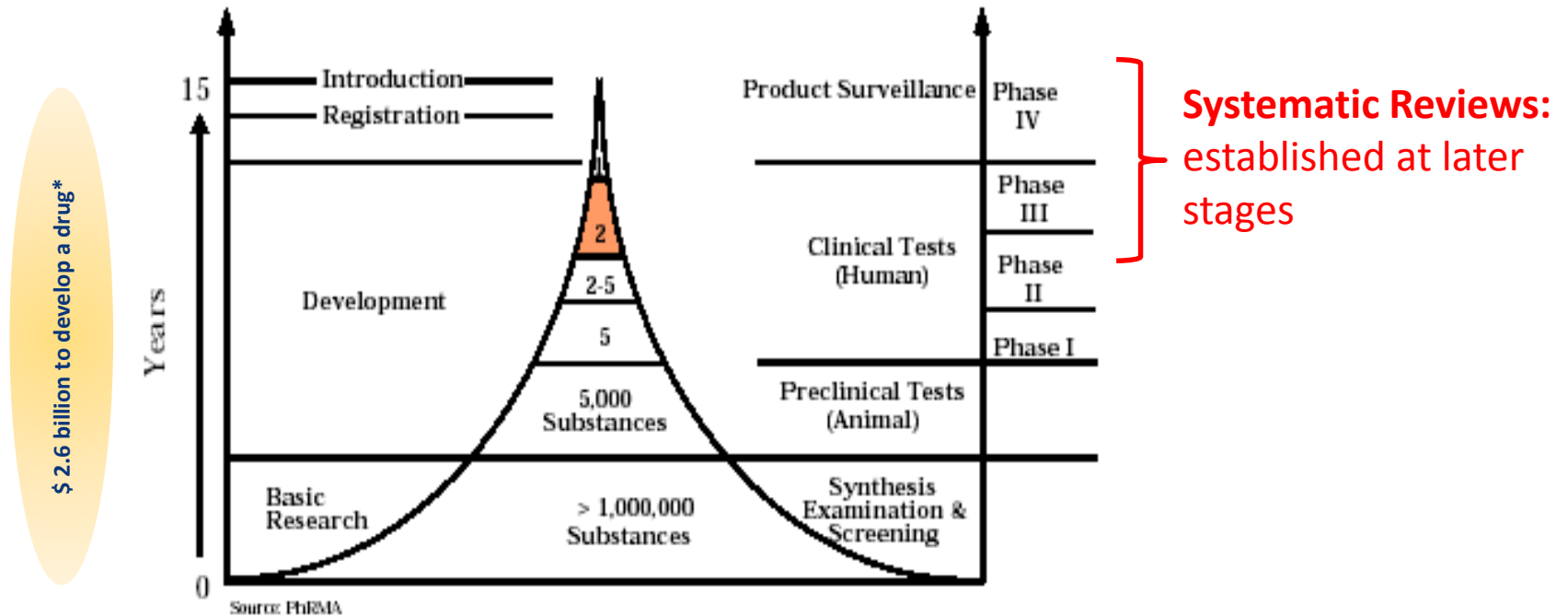
An Industry Perspective on the Utility of Systematic Reviews

Launch of the CAMARADES-NC3Rs Systematic Review Facility (SyRF), 30 March 2017

Thomas Steckler

The views expressed in this presentation are solely those of the individual authors, and do not necessarily reflect the views of their employers.

Development of Drugs: Complex and Time Consuming

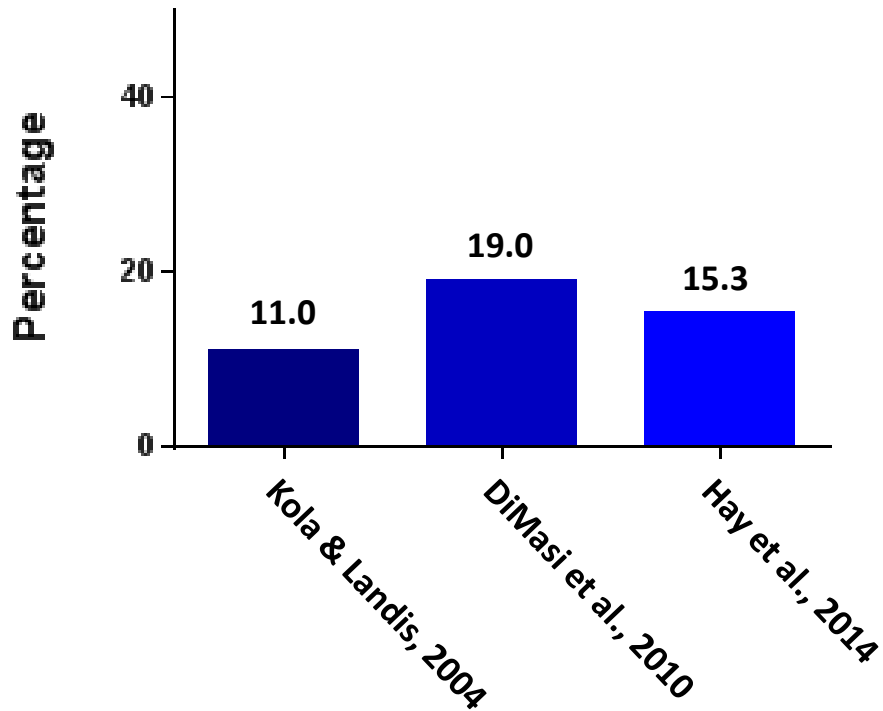


- **58** preclinical projects needed on average to achieve 1 launch
- **93** preclinical projects needed to have 80% likelihood to achieve one launch

(Decision Analysis & Portfolio Management, 2005)

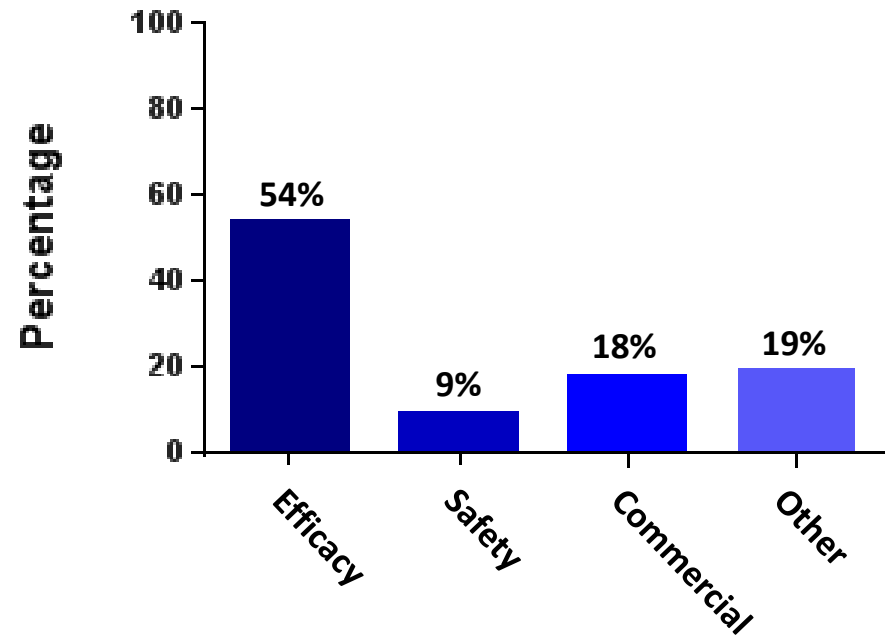
Probability of FDA Approval for Drugs in Phase 1


Low Probability for Lead Indication Across 3 Studies



Reason for Attrition in Phase 3

Hay et al., 2014





**Can
Systematic
Reviews
help?**

Systematic Reviews at Janssen Established in Clinical Research and Health Economics

CMRO
Current Medical Research and Opinion

ISSN: 0306-7995 (Print) 1473-4877 (Online) Journal homepage: <http://www.tandfonline.com/doi/cmro20>

Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis

Katerina Pagadimitropoulou, Carla Vossen, Andreas Karabis, Christina Donatti & Nicole Kubitz

Smith-Palmer et al. BMC Infectious Diseases
DOI 10.1186/s12879-015-0749-8

BMC Infectious Diseases
Open Access

RESEARCH ARTICLE

Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits

Jayne Smith-Palmer^{1*}, Karin Cerni² and William Valentine³

Neuropsychiatric Disease and Treatment
Dovepress
open access to scientific and medical research

REVIEW

Global economic burden of schizophrenia: a systematic review

This article was published in the following Dove Press journal: Neuropsychiatric Disease and Treatment
18 February 2016

Yi Yi Hong¹
Li Teshi¹
Ji Bin-Chia Wu¹
chai Kotirum¹
in-Fang Chiou¹
Iorn Chaiyakunapruk^{1,3-5}

Background: Schizophrenia is one of the top 25 leading causes of disability worldwide in 2013. Despite its low prevalence, it is not only for patients but also for society in terms of disease burden investigation in decision making. This study aims to identify the burden of schizophrenia in terms of economic burden.

CNS Drugs (2015) 29:637-658
DOI: 10.1007/s00263-015-0269-4

SYSTEMATIC REVIEW

The Use of Continuous Treatment Versus Placebo or Intermittent Treatment Strategies in Stabilized Patients with Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with First- and Second-Generation Antipsychotics

Marc De Hert¹ · Jan Sermon² · Paul Geerts³ · Kristof Vansteelandt¹ · Joseph Peuskens⁴ · Johan Detraux⁵

PLOS ONE

RESEARCH ARTICLE

Current Developments in Dementia Risk Prediction Modelling: An Updated Systematic Review

Eugene Y. H. Tang^{1*}, Stephanie L. Harrison¹, Linda Errington¹, Mark F. Gordon¹, Pieter Jellie Visser^{1,2}, Gerald Novak³, Carole Dufouir⁴, Carol Brayne⁵, Louise Robinson¹, Lenore J. Launer⁶, Blossom C. M. Stephan¹

Clinical and Experimental Gastroenterology
Dovepress
open access to scientific and medical research

REVIEW

Systematic review: treatment pattern and clinical effectiveness and safety of pharmaceutical therapies for Crohn's disease in Europe

This article was published in the following Dove Press journal: Clinical and Experimental Gastroenterology
5 October 2016
Number of items this article has been viewed

Filippo Lelli¹
Solomon Nuhoho²
Xin Ying Lee³
Weiwei Xu⁴

Background: Although many clinical trials have been conducted in the field of Crohn's disease (CD), whether the trial results were representative of daily practice by studies conducted in real-world settings. **Aim:** This study aims to identify how CD is treated and what are the clinical outcomes of the pharmaceutical therapies of CD in real-world settings.

JME
Journal of Medical Economics
Taylor & Francis

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: <http://www.tandfonline.com/doi/jme20>

Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD

Thomas R. Einarson, Basil G. Berezka, T. Anders Nielsen, Jan Van Laer & Michiel E. H. Hemels

ClinicoEconomics and Outcomes Research
Dovepress
open access to scientific and medical research

REVIEW

Cost-effectiveness of bortezomib for multiple myeloma: a systematic review

This article was published in the following Dove Press journal: ClinicoEconomics and Outcomes Research
2 May 2016
Number of items this article has been viewed

Wendong Chen¹
Yicheng Yang²
Yi Chen³
Fen Du⁴
Huan Zhan¹

Objectives: To review published cost-effectiveness analyses (CEAs) assessing bortezomib (BTZ) for multiple myeloma (MM) and explore possible bias affecting the cost-effectiveness of BTZ. **Methods:** Literature was searched for published CEAs assessing BTZ or BTZ-containing regimens for MM from 2003 to 2015. The reported incremental cost-effectiveness ratios (ICERs)

Pain Medicine 2012; 13: 575-595
Wiley Periodicals, Inc.

NEUROPATHIC PAIN SECTION


Original Research Article

Placebo Response Changes Depending on the Neuropathic Pain Syndrome: Results of a Systematic Review and Meta-Analysis

M. Soledad Cepeda, MD, PhD,*
Jesse A. Berlin, ScD,* C. Yuying Gao, MD, PhD,¹
Frank Wiegand, MD, PhD,¹ and D. Russell Wads, PhD¹

Outcome Measures. Pain intensity and responder rates (proportion reporting $\geq 50\%$ pain relief). Meta-regression models were built.

But Rather Limited Use in Other Areas Related to Drug Development

 **SOT** | Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 152(1), 2016, 10-16
doi: 10.1093/toxsci/kfw059
Advance Access Publication Date: May 5, 2016
Forum Article


FORUM ARTICLE

The Emergence of Systematic Review in Toxicology

Martin L. Stephens,^{a,1} Kellyn Betts,^b Nancy B. Beck,^c Vincent Cogliano,^d Kay Dickersin,^e Suzanne Fitzpatrick,^f James Freeman,^g George Gray,^h Thomas Hartung,^{a,i} Jennifer McPartland,^j Andrew A. Rooney,^k Roberta W. Scherer,^e Didier Verloo,^l and Sebastian Hoffmann^m

Health Policy 100 (2011) 4-17

Contents lists available at ScienceDirect

 **ELSEVIER**

Health Policy

journal homepage: www.elsevier.com/locate/healthpol



Review


The cost of drug development: A systematic review

Steve Morgan^{a,b,*}, Paul Grootendorst^{c,d}, Joel Lexchin^{e,f}, Colleen Cunningham^a, Devon Greyson^a

Research 

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philippa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E. Mignini, Pradeep Jayaram, Khalid S Khan

 **Assessment of somatic *k*-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer**

Helena Linardou, Issa J Dahabreh, Dimitra Kanaklopiti, Fotios Siannis, Dimitrios Bafaloukos, Paris Kosmidis, Christos A Papadimitriou, Samuel Murray

Summary
Background Somatic mutations of the *k*-RAS oncogene have been assessed as a mechanism of de-novo resistance to epidermal growth factor receptor (EGFR) tyrosine-kinase inhibition in patients with non-small-cell lung cancer (NSCLC), and to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer (mCRC). The aim of this systematic review and meta-analysis was **to assess if *k*-RAS mutations represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in mCRC and NSCLC.**

Lancet Oncol 2008; 9: 962-72
Published Online

Review | Clinician's Corner

August 15, 2007

High-Density Lipoprotein as a Therapeutic Target A Systematic Review

Inder M. Singh, MD, MS; Mehdi H. Shishehbor, DO, MPH; Benjamin J. Ansell, MD

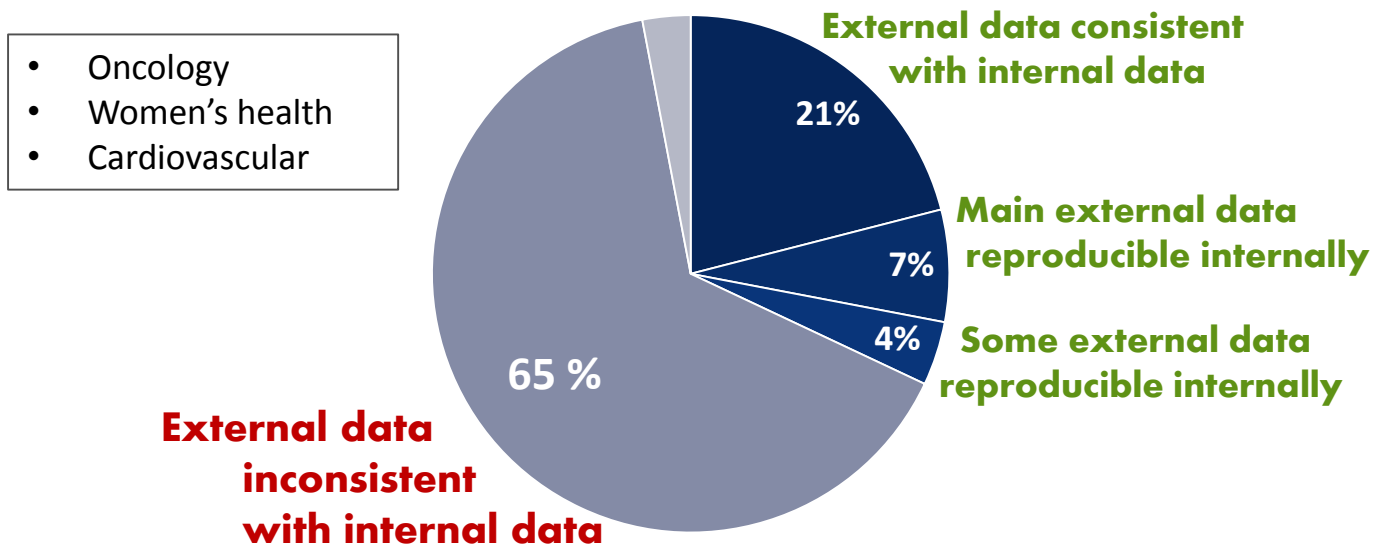
> Author Affiliations

JAMA. 2007;298(7):786-798. doi:10.1001/jama.298.7.786

Unaware of any SR in drug discovery / preclinical development at Janssen

Despite Background of Poor Reproducibility of Published Preclinical Data

Majority of published studies not reproduced by Bayer



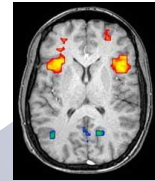
Prinz et al., Nature Rev Drug Disc, 2011

Aggregation of available information in a neutral manner reduces risk of bias and cherry picking

Should We Use Systematic Reviews Earlier? Example Target Validation

Tractability?

Viable starting points?
Freedom to operate?



Medical Need?

Supportive Clinical Data?

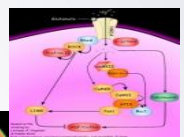
Evidence for efficacy and safety in patients?
Evidence for genetic association between target and disease?
Evidence for target linked to disease phenotype?

Market?

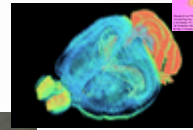


Supportive In Vivo Data?

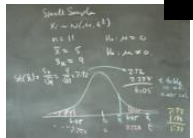
Evidence for predictive validity of models?
Evidence for models with disease phenotype?
Evidence for efficacy of preclinical target manipulation?



Evidence for Conserved Cross-Species Characteristics?



Evidence for Relevant Expression Pattern?



Plausible Hypothesis?

What Prevents Systematic Review Early On for Target Validation?

Limited data and limited transparency

- Preference for new targets in the hope to develop first in class drugs
- Insufficient public data on novel target leaves review inconclusive

Limited availability of unbiased data

- Low likelihood of publication of negative data, especially for new findings on novel mechanism of action/target
- ➔ Leads to overestimation of the role of a target in a disease process

Long timelines to completion

- Often industry requires rapid decisions about the validity of a target
- Time required for a Systematic Review may be prohibitive

Where could Systematic Review be Enabling in Drug Discovery ? Example Assay Validation

Research

BMJ

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram, Khalid S Khan

Study selection Animal studies for interventions with unambiguous evidence of a treatment effect (benefit or harm) in clinical trials: head injury, antifibrinolytics in haemorrhage, thrombolysis in acute ischaemic stroke, tirilazad in acute ischaemic stroke, antenatal corticosteroids to prevent neonatal respiratory distress syndrome, and bisphosphonates to treat osteoporosis.

Conclusions Discordance between animal and human studies may be due to bias or to the failure of animal models to mimic clinical disease adequately.

Potential Utilities:

- **Scientific tool:** *Phenotypic screening of compounds based on effects obtained in model systems
(Routine) efficacy / safety / tox models*
- **Management tool:** *Decision-making based on predictions of clinical efficacy and absence of safety/tox issues of lead compounds*
- **Ethical tool:** *Animal study protocol approval by ethical committees*

The Problem: You Get Out What You Put In

Effects of Long-Term Omega-3 Fatty Acid Supplementation on Cognition in Animal Models of Alzheimer's Disease

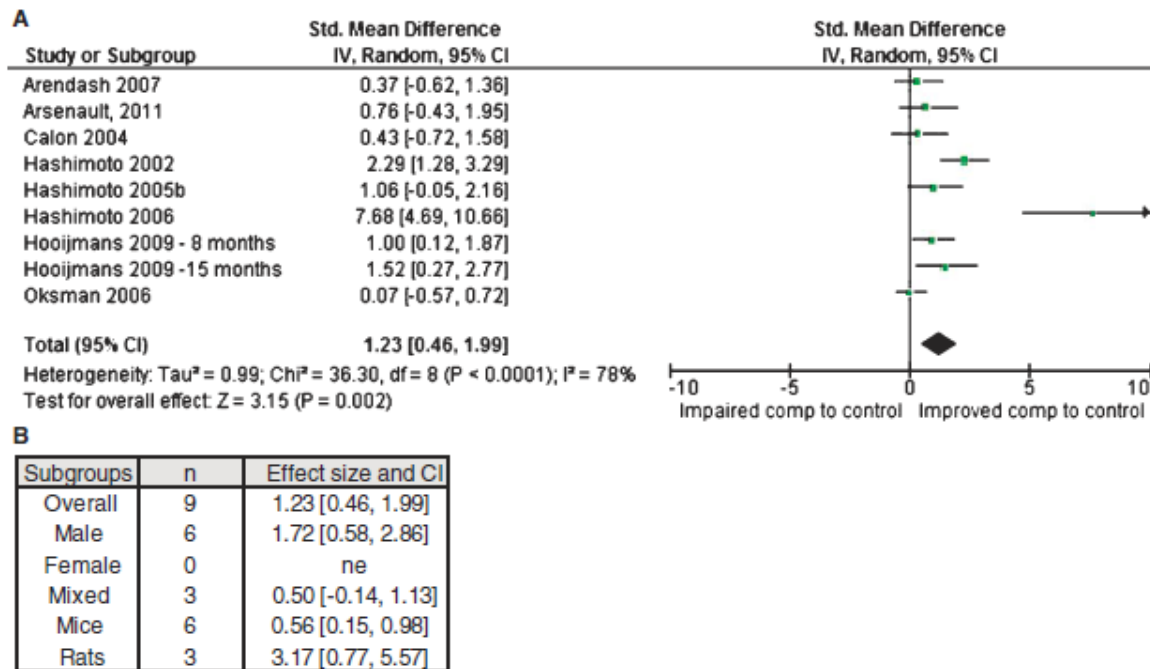


Fig. 2. (a) Forest plot (effect size and 95% CI) and (b) subgroup analysis of individual studies of omega-3 FA supplementation on cognition in experimental animal models of Alzheimer's disease.

Included Cognition Studies

Study Characteristics (from Table 2 in Hooijmans et al., p. 195-195):

Study	Species	AD model	Sex	Supplement	Route of administration	Start supplementation	Amount of supplement (treated/control)	Duration of supplementation	Outcome measures
Arendash [43]	Mouse	A β PP/PS1 2 \times TgAD	?	n-3 fatty acids	Diet	2 months	13%/2.76	5.5 months	Cognition: MWM, circular platform platform recognition, Y-maze, RAWM
Arsenault [54]	Mouse	A β PP/PS1/tau; 3 \times TgAD	?	DHA	Diet	4 months	0.6%/0	8-10 months	Cognition: object recognition
Calon [45]	Mouse	tg2576	M+F	DHA	Diet	17 months	0.6%/<0.01%	103 days	Cognition: MWM
Hashimoto [48]	Rat	A β infused rats	M	DHA in gum arabic solution	Oral	25 weeks	300 mg/kgBW/day vs 0	15 weeks	Cognition: avoidance learning
Hashimoto [50]	Rat	A β infused rats	M	DHA in gum arabic solution	oral	26 weeks	300 mg/kgBW/day vs 0	12 weeks	Cognition: Radial Arm Maze
Hashimoto [46]	Rat	A β infused rats	M	DHA in gum arabic solution	oral	26 weeks	300mg/kgBW/day vs 0	12 weeks	Cognition: Radial Arm Maze
Hashimoto [47]	Rat	A β infused rats	M	DHA in gum arabic solution	oral	25 weeks	300mg/kgBW/day vs 0	12 weeks	Cognition: avoidance learning
Hooijmans [39]	Mouse	A β PP/PS1 2 \times TgAD	M	DHA + EPA	diet	2 months	0.4%/0%	6 or 13 months	Cognition: MWM, circular platform, reverse MWM
Oksman [53]	Mouse	A β PP/PS1 2 \times TgAD	M	DHA	diet	6 months	0.5%/0%	4 months	Cognition: MWM

No. tests truly predictive:

Tasks used (from Hooijmans et al., p. 198):

Task	Number of studies
Morris water maze	5
Avoidance learning	2
Object recognition	1
Radial arm maze	1

0

But: It doesn't work in patients!

Authors' conclusions

We found no convincing evidence for the efficacy of omega-3 PUFA supplements in the treatment of mild to moderate AD. This result was consistent for all outcomes relevant for people with dementia. Adverse effects of omega-3 PUFAs seemed to be low, but based on the evidence synthesised in this review, we cannot make a final statement on tolerability. The effects on other populations remain unclear.



Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A. Omega-3 fatty acids for the treatment of dementia. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD009002. DOI: 10.1002/14651858.CD009002.pub3.

The Status Quo - Time to Change?

The Classical Approach: Narrative Reviews

- Mainly descriptive overviews (Compound Monographs, IBs, journal articles)
- Often selective literature searches
- Potentially biased due to focus on a subset of studies, based on author selection

Possible Future Approach: Systematic Reviews

- Comprehensive aggregation of available information in a neutral manner to reduce risk of bias and cherry picking
- Pre-defined quality criteria, upfront plan and search strategy
- Meta-analysis if possible and required to provide a quantitative estimate or summary effect size

A Personal View on the Utility of Systematic Reviews in Industry

Data must be fit for purpose

- Availability of qualified data sets / publications
 - ➔ Not suited for all areas of drug development

Process must be fit for purpose

- Manageable workload
 - ➔ Graded approach: aggregate data analysis as default, individual data if required
 - ➔ Limited resource needs ($\ll 1$ FTE), automated if possible
- Acceptable timelines
 - ➔ 3 months max.

Users must understand the limitations

- Overestimation of effect sizes due to biases in original reports
- Still requires judgement whether data are pertinent

Can SyRF offer solutions?

Meeting the conditions above, SRs would facilitate evidence-based decisions, also in the earlier stages of DD, and should be more widely employed !