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Disease-modifying pharmacological treatments for amyotrophic lateral sclerosis/motor neuron disease: an overview of intervention reviews (Protocol)

Balendra R, Orrell RW, Pearce N, Al-Chalabi A

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[Overview of Reviews Protocol]

Disease-modifying pharmacological treatments for amyotrophic lateral sclerosis/motor neuron disease: an overview of intervention reviews

Rubika Balendra[1,2], Richard W Orrell[3], Neil Pearce[4], Ammar Al-Chalabi[5]

[1]Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK. [2]UK Dementia Research Institute at UCL, UCL Cruciform Building, London, UK. [3]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK. [4]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK. [5]Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, London, UK

Contact: Ammar Al-Chalabi, ammar.al-chalabi@kcl.ac.uk.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (overview). The objectives are as follows:

To summarise the evidence from Cochrane and non-Cochrane systematic reviews of pharmacological disease-modifying treatments for amyotrophic lateral sclerosis/motor neuron disease.

BACKGROUND

Description of the condition

Amyotrophic lateral sclerosis (ALS), which is the most common form of motor neuron disease (MND), is a fatal neurodegenerative disorder characterised by the progressive loss of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord (Brown 2017; Kiernan 2011). Most people with ALS die within three to five years of diagnosis, primarily due to respiratory failure, although a small proportion live for longer than 10 years (Turner 2003). ALS is on a clinical, genetic and pathological spectrum with frontotemporal lobar dementia (FTLD), which is characterised by memory loss, cognitive and behavioural dysfunction, and pathologically by degeneration of the frontal and temporal cortices (Ling 2013). In people with European ancestry, the lifetime risk of ALS is one in 300 (Alonso 2009; Johnston 2006), with an estimated incidence of two per 100,000 population and prevalence of five per 100,000 population (Chio 2013). ALS is predominantly a disease of ageing, with the risk of developing the disease increasing with age; the peak age of incidence occurs between 50 and 70 years, although the age of onset is wide with 10% of people having a younger age of onset (less than 45 years) (Turner 2013). In addition, men are more commonly affected than women (Brown 2017). The majority of ALS is classified as sporadic disease, but in 10% to 15% of cases there is a familial inheritance pattern (Brown 2017).

The diagnosis of ALS is made based on clinical findings. The patient history and clinical examination reveal features of progressive upper and lower motor neuron dysfunction, without sensory or autonomic features, and in the absence of other disease processes that could explain the clinical findings. Patients can present with a variety of symptoms, but commonly the disease begins with focal weakness, spreading to affect other regions (Al-Chalabi 2016). Approximately 30% of patients initially present with bulbar disease, features of which include dysphagia, dysarthria and sialorrhoea. The underlying causes of sialorrhoea are tongue spasticity and weakness of the facial, mouth and pharyngeal muscles; loss of oropharyngeal co-ordination and function; and subsequent inability to swallow secretions (James 2022). The revised El Escorial criteria are used to diagnose ALS; however, these tend to be used for selecting and stratifying patients for clinical trials and research studies, with three diagnostic categories: clinically definite, probable or possible ALS (Brooks 1994; Brooks 2000). Furthermore, the Awaji criteria detail specific features on electromyography (EMG) investigations, which can greatly assist the diagnosis (de Carvalho 2008). The El Escorial diagnostic criteria have recently been superseded by the Gold Coast criteria for the diagnosis of ALS (Shefner 2020). Cognitive impairment can occur in up to 80% of people with ALS (Crockford 2018), and up to 15% of people with ALS have a clinical diagnosis of FTD (Ling 2013; Ringholz 2005).

The neurobiology underlying disease mechanisms in ALS is complex, and there have been significant discoveries unravelling the underlying disease process over recent decades. Key genetic findings have transformed our understanding of the disease, and several genes are now implicated in the disease process. Hexanucleotide GGGGCC expansions in the *C9orf72* gene are the most frequent genetic cause of ALS, and *SOD1* mutations also account for a relatively large proportion of cases (Al-Chalabi 2012; DeJesus-Hernandez 2011; Marangi 2015; Renton 2011; Renton 2014). The pathological hallmark of ALS and a large proportion of FTLD is cytoplasmic inclusions of transactive response DNA-binding protein (TDP-43), a highly conserved and ubiquitous ribonucleic acid (RNA)- and DNA-binding protein, which becomes mislocalised from the nucleus and ubiquitinated and hyperphosphorylated in disease (Buratti 2001; Buratti 2004; Mercado 2005; Neumann 2006). *TDP-43* and *FUS* mutations also lead to ALS or FTD (or both) (Sreedharan 2008; Vance 2009), and several other genes have been implicated in these diseases, including *PGRN*, *UBQLN2*, *SQSTM1*, *PFN1*, *ANG*, *VCP*, *MATR3*, *TUB4A* and *TBK1* (Abel 2012; Al-Chalabi 2017; ALSoD 2021). Overall, the implicated genes suggest dysregulation of protein homeostasis, RNA metabolism and cytoskeletal dysfunction as critical to molecular pathogenesis in the disease (Ling 2013). In vitro and in vivo models of disease and pathological studies have yielded insights into autonomous and non-autonomous cellular processes which become dysfunctional in ALS. These include autophagy, oxidative stress, the unfolded protein response, the ubiquitin-proteasome system, synaptic activity and excitotoxicity, mitochondrial function, RNA transport and processing, axonal function and transport, and the function of glia, including astrocytes and microglia (Brown 2017; Robberecht 2013). Therapeutic strategies have been developed to mitigate several of these dysfunctional processes; however, thus far few have yielded positive results in Phase II/III clinical trials, and the reasons for this are multifactorial (Mitsumoto 2014). The revised Airlie House consensus guidelines, and the more recent Gold Coast criteria, should standardise and improve the quality of both preclinical and clinical studies, with the ultimate goal of maximising the chances of finding effective therapies (van den Berg 2019).

The National Institute for Health and Care Excellence (NICE) has published comprehensive guidelines for the assessment and management of ALS (NICE 2019). Importantly, ALS should be managed by a multidisciplinary clinical team which includes a neurologist, specialist nurse, dietician, physiotherapist, occupational therapist, respiratory physiologist, and speech and language therapist, and the team should have close contact with several other services, including palliative care support, gastroenterology, respiratory ventilation support, clinical psychology, and orthotics and assistive technology. Currently, the mainstay of treatment is optimising quality of life through the management of symptoms, nutrition and respiratory failure, with consideration of gastrostomy and ventilatory support, and implementation of end of life care. Riluzole is a licensed disease-modifying treatment for ALS, and prolongs life by two to three months at 12 months into the disease duration (Bensimon 1994; Lacomblez 1996; Miller 2012), with survival benefits demonstrated at early and late stages of the disease (De Jongh 2019; Fang 2018; Thakore 2020). Non-invasive ventilatory support can also prolong life by approximately six months in some patient subgroups (Bourke 2006; Radunovic 2017). Edaravone, an antioxidant drug, has been shown to slow the rate of functional decline as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) in one Phase III trial (Writing Group 2017). It has now been licensed for people with ALS in Japan, the USA, Canada, South Korea and Switzerland.

Description of the interventions

This review is an overview of Cochrane and non-Cochrane systematic reviews of disease-modifying pharmacological

treatments for ALS, which are those hypothesising to target the underlying disease process in ALS/MND. This review will not include pharmacological and non-pharmacological treatments for symptoms of ALS, which is the subject of a previous Cochrane overview of reviews (Ng 2017).

How the intervention might work

The interventions aim to target underlying disease processes involved in ALS.

Neurotrophic factors

A lack of trophic factors, which are molecules promoting cell survival and differentiation, may underlie the degeneration of motor neurons in ALS. Therefore, the use of trophic factors such as ciliary neurotrophic factor (CNTF), could lead to increased motor neuron survival (Mitsumoto 1994; Selvaraj 2013; Sendtner 1992). Furthermore, recombinant human insulin-like growth factor I (rhIGF-I) has neurotrophic effects on motor neurons in disease models (Hantai 1995). On the basis of promising preclinical studies, these therapies have progressed to clinical trials in people with ALS/MND.

Antioxidants and mitochondrial function

Oxidative stress contributes to motor neuron degeneration in ALS, where free radicals accumulate and endogenous antioxidant defence mechanisms are unable to prevent their effects and oxidative damage (Goodall 2006). This leads to damage to nucleic acids, proteins and lipids, and ultimately cell death. Antioxidant enzymes, such as superoxide dismutase, reduce the effects of these free radicals. Therefore, antioxidant agents could be utilised as therapies in ALS to reduce free radical oxidative damage. Antioxidants can be derived from nutrient sources, and include vitamins C and E, and carotenes.

Furthermore, ALS affects mitochondrial energy metabolism and function (Goodall 2006; Robberecht 2013). Creatine is a nitrogenous organic acid that has antioxidant effects and may improve mitochondrial function (Adhihetty 2008).

Excitotoxicity

Imbalances in the excitatory neurotransmitter glutamate and inhibitory neurotransmitter gamma aminobutyric acid (GABA) may lead to ALS, by causing excitotoxicity and cell death (Rao 2004). Increased levels of GABA and glutamate have been reported in the cerebrospinal fluid (CSF) of people with ALS (Niebroj-Dobosz 1999; Shaw 1995).

Riluzole blocks presynaptic glutamate release, and may therefore prevent glutamate excitotoxicity. GABA modulators, such as gabapentin, which has conformational properties similar to the structure of GABA, may also act in this pathway.

Other mechanisms

Other potential mechanisms of treatment include anti-inflammatory and anti-apoptotic agents.

Why it is important to do this overview

There are six published Cochrane Reviews in the Cochrane Library for pharmacological disease-modifying treatments for ALS (Beauverd 2012; Bongioanni 2004; Diana 2017; Miller 2012; Orrell 2007; Pastula 2012). An overview of the Cochrane and non-Cochrane systematic reviews of treatments for ALS in one document will enable clinicians, researchers and policymakers to access a single source of information. An overview of reviews will help to crystallise the information from systematic reviews, so that the effect of interventions for ALS and the certainty of the evidence are presented in an accessible format. Where possible, it will enable direct and indirect comparison of the effectiveness of the different interventions included. The results of this overview may help to inform best practice and areas where further research is needed.

OBJECTIVES

To summarise the evidence from Cochrane and non-Cochrane systematic reviews of pharmacological disease-modifying treatments for amyotrophic lateral sclerosis/motor neuron disease.

METHODS

We will complete the overview according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Pollock 2021).

Criteria for considering reviews for inclusion

Types of reviews

As suggested by the *Cochrane Handbook for Systematic reviews of Interventions* (Pollock 2021), we will consider all Cochrane and non-Cochrane systematic reviews of randomised controlled trials (RCTs) and quasi-RCTs (such as alternate allocation) of disease-modifying treatments for ALS/MND.

Cochrane Reviews have:

- predefined objectives;
- predefined criteria for eligibility of evidence;
- an objective systematic search for evidence applying predetermined inclusion and exclusion criteria; and
- explicit and systematic methods for synthesising evidence which attempt to reduce bias.

Non-Cochrane systematic reviews may cover relevant interventional comparisons and data that are not available in Cochrane Reviews. We will also identify ongoing systematic reviews and any systemic review updates that are in progress, and update the overview as these are published.

Furthermore, if during data collection we find RCTs of other therapies that have not yet been included in a Cochrane Review, we will draw the attention of Cochrane Neuromuscular to the existence of the studies so that they could be included in an existing or new review.

Types of participants

We will include participants with a diagnosis of ALS/MND. Some trials will state whether the included participants met the World Federation of Neurology El Escorial diagnostic criteria for ALS/MND or the revised diagnostic criteria, but other trials performed prior to the existence of these criteria may not. We will quantify the number of trials predating the World Federation of Neurology El Escorial diagnostic criteria, and include these with the other trials, with the

understanding that some of the participants may not have met the criteria. We will include participants of all ages, all types of onset and familial or sporadic disease.

Types of interventions

We will include all types of disease-modifying pharmacological treatment for the underlying disease process in ALS/MND. Where possible, we will try to compare these interventions to each other and to placebo or usual care. We will not be including treatments for the symptoms of the disease, as these are featured in a separate Cochrane overview of symptomatic treatments (Ng 2017).

Types of outcomes

The outcome measures we will use reflect those used in the Cochrane systematic reviews and those most relevant to people with ALS.

Primary outcome

- Tracheostomy-free survival

Secondary outcomes

- Functional scores measured by a validated functional rating scale
- Quality of life and health-related quality of life
- Muscle strength
- Respiratory function or forced vital capacity (FVC) or vital capacity (VC)
- Adverse effects of the treatment
- Neurophysiological measurements: motor unit number estimate (MUNE) and neurophysiological index

These are all measures that are frequently used in ALS clinical trials. For functional scales, quality of life scores and muscle strength scores, we will prioritise scales that have been validated as having good reproducibility, face validity and correlation with other scales measuring the same attribute. The revised ALSFRS-R is a commonly used, validated, functional scale which uses a 4-point scoring system for 12 questions to assess function in a range of domains of speech; salivation and swallowing; turning in bed; walking; climbing stairs; dressing and hygiene; handwriting; cutting food; and respiratory insufficiency, dyspnoea and orthopnoea. This is a good example of an appropriate functional scale.

We will also report on adverse effects of the treatment, including those that are fatal or lead to severe morbidity or hospitalisation, and on more common adverse effects of the treatment. Where there is information regarding the number of participants who have withdrawn from the trial due to adverse effects, we will also report on this.

Search methods for identification of reviews

The Cochrane Neuromuscular Information Specialist will search the following sources without any language, date, document type, or publication status limitations:

- Cochrane Database of Systematic Reviews via the Cochrane Library (Appendix 1);
- MEDLINE via OvidSP (1946 to search date; Appendix 2);
- Embase via OvidSP (1974 to search date; Appendix 3);
- Epistemonikos (until search date; Appendix 4).

We will use the modified version of Scottish Intercollegiate Guidelines Network's systematic review search filters for MEDLINE and Embase.

The Information Specialist will search for errata or retractions related to included reviews, and the overview authors will examine retrieved retraction statements and errata.

We will record the search process in sufficient detail to prepare a PRISMA study flow diagram.

Data collection and analysis

We will use the following methods of data collection and data analysis in this overview of systematic reviews.

Selection of reviews

Two overview authors (RB and RWO) will select Cochrane and non-Cochrane systematic reviews suitable for inclusion and a third overview author will act as arbiter in the event of disagreements. We will document reasons for exclusion in a Characteristics of excluded reviews table. Overview authors will not decide selection of any reviews of which they are an author.

Data extraction and management

Two overview authors (RB and RWO) will independently collect data from published Cochrane and non-Cochrane systematic reviews of pharmacological disease-modifying treatments for ALS. Overview authors will not collect data from any reviews of which they are an author. We will use the data collection and synthesis methodology outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Pollock 2021). We will collect data using a standardised data collection form, which we will pilot prior to use. If we require further information, we will contact the authors of the relevant systematic review, and if necessary, the authors of the original study. If there are overlapping reviews for the same research question, we will assess if they have overlapping primary studies. We will include all non-overlapping reviews, and select the highest quality systematic review for groups of overlapping reviews. Each author will use the revised Assessment of Multiple Systematic reviews (AMSTAR 2) tool to assess each overlapping review (Shea 2009; Shea 2017). Based upon their interpretation of the results of this tool, each overview author will assess which is the highest quality. We will discuss any discrepancies to reach a consensus, and for any disagreements, a third overview author will act as arbiter.

We will collect information on types and numbers of participants, whether they meet World Federation of Neurology El Escorial diagnostic criteria for ALS, types of interventions covered in the review, the outcome measures reported and length of follow-up.

We will enter data into Review Manager Web (RevMan Web 2022). We will complete Characteristics of reviews tables for included reviews, reviews awaiting assessment and ongoing reviews.

Assessment of methodological quality of included reviews

Two overview authors, neither of whom will be an author of the included review, will independently assess the methodological quality of each review included in the overview using the AMSTAR

2 tool. This tool has acceptable inter-rater agreement, construct validity and feasibility (Shea 2009; Shea 2017). The items of this tool will be collected into a table, and all 12 domains specified in the AMSTAR 2 tool will be addressed. If there are disagreements in the assessments, a third overview author will act as arbiter. We will not repeat the assessment of eligibility, the assessment of risk of bias, or meta-analyses from the included reviews, nor identify any additional studies, or extract additional outcomes from individual studies included in the original systematic reviews.

Risk of bias of primary studies included in reviews

Where a risk of bias assessment is already available in the systematic review, we will extract this. Otherwise, we will use a comprehensive assessment of risk of bias using the Cochrane RoB 1 tool and assessing risk of bias domains as detailed in the methodology outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017; Pollock 2021).

If there are discrepancies in risk of bias assessments or data in overviews that have collected data from the same primary study, we will return to the primary study to verify the accuracy of extracted data or risk of bias assessment, and perform a reanalysis.

Certainty of evidence in included reviews

Two overview authors will independently assess the certainty of the evidence in the included reviews using the GRADE approach (Guyatt 2008). Where a GRADE assessment is already available in the systematic review, we will extract this. The overview authors will check any criteria used by the review authors for making assessments and whether we agree with the GRADE assessments made within the reviews to ensure consistency across reviews. If there are inconsistencies in GRADE approaches across reviews, the overview authors will independently make their own assessments for each outcome of each review. The GRADE approach enables evaluation of the certainty of evidence, according to four grades: high, moderate, low and very low. These gradings are influenced by any study limitations; inconsistencies in the data (heterogeneity); uncertainty regarding direct impact of the findings; imprecise or sparse data; reporting bias (which are the five reasons for downgrading the evidence); or large magnitude of effect, evidence of association or dose response; and any confounders working to reduce the demonstrated effect or increase the effect, if no effect was observed (three reasons for upgrading the evidence).

If there are disagreements in the GRADE assessments, a third overview author will act as arbiter.

Data synthesis

The main method for presenting the data will be as a narrative review. We will present narrative summaries of the outcome data from each included systematic reviews in turn. We will use the GRADE approach to present the evidence for each intervention from each systematic review. We will not explore subgroups.

Summary of findings

We will collate the information in an overview of systematic reviews presented as a summary of findings table, which will include references to indicate which outcome data come from which systematic review. This table will include the participants, interventions studied, comparisons made, outcomes and outcome measures used, and the certainty of the evidence for each outcome according to the GRADE system. We will present descriptive data at the level of each systematic review. If data are missing from the systematic review, we will note the gap in coverage in the Overview. We will not repeat the meta-analyses from the included reviews, unless there have been discrepancies in risk of bias assessments or data in reviews that have collected data from the same primary study. In this case, we will return to the primary study to verify the accuracy of extracted data or risk of bias assessment, and perform a repeat meta-analysis.

Assessment of bias in conducting the overview

We will conduct the overview according to this published protocol, and report any deviations from it in the 'Differences between protocol and review' section.

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APPENDICES

Appendix 1. Cochrane Database of Systematic Reviews search strategy

[mh "Motor Neuron Disease"] or (Motor Neuron Disease* or Motor Neurone Disease* or Motoneuron Disease* or Motoneurone Disease or Amyotrophic Lateral Sclerosis):ti,ab

in Cochrane Reviews and Cochrane Protocols

Appendix 2. MEDLINE search strategy

1 exp Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ or (Motor Neuron Disease* or Motor Neurone Disease* or Motoneuron Disease* or Motoneurone Disease or Amyotrophic Lateral Sclerosis).ti,ab.

2 Meta-Analysis as Topic/ or Meta-Analysis/ or exp Review Literature as Topic/ or (Meta Analy$ or Metaanaly$ or (Systematic adj (Review$1 or Overview$1))).tw. or (Cochrane or Embase or CINAHL or CINHAL or Science Citation Index or MEDLINE or PubMed or Reference List$ or Bibliograph$ or Hand-Search$ or Relevant Journals or Manual Search$).ab. or (Review/ and (Selection Criteria or Data Extraction).ab.)

3 Comment/ or Letter/ or Editorial/

4 Animal/ not (Animal/ and Human/)

5 (1 and 2) not (3 or 4)

Appendix 3. Embase search strategy

1 exp Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ or (Motor Neuron Disease* or "Motor Neurone Disease* or Motoneuron Disease* or Motoneurone Disease or Amyotrophic Lateral Sclerosis).ti,ab.

2 exp Meta Analysis/ or ((Meta adj Analy$) or Metaanalys$).tw. or (Systematic adj (Review$1 or Overview$1)).tw. or (Cochrane or Embase or CINAHL or CINHAL or Science Citation Index or MEDLINE or PubMed or Reference List$ or Bibliograph$ or Hand-Search$ or Relevant Journals or Manual Search$).ab. or ((Data Extraction or Selection Criteria).ab. and Review.pt.)

3 (Letter or Editorial).pt.

4 Animal/ not (Animal/ and Human/)

5 (1 and 2) not (3 or 4)

Appendix 4. Epistemonikos search strategy

Advanced Search

(title:(Motor Neuron Disease OR Amyotrophic Lateral Sclerosis) OR abstract:(Motor Neuron Disease OR Amyotrophic Lateral Sclerosis))

Publication type: Broad Synthesis or Structured Summary or Systematic Review

CONTRIBUTIONS OF AUTHORS

RB drafted the protocol.

RO: provided comments and approved the submission.

NP: provided comments and approved the submission.

AAC: provided comments and approved the submission.

DECLARATIONS OF INTEREST

RB is an author of a potentially eligible Cochrane Review update in development entitled "Antioxidant treatment for amyotrophic lateral sclerosis or motor neuron disease". She declares institutional grants from the University College London (UCL) Leonard Wolfson Experimental Neurology Centre from 2013 to 2018 and the Wellcome Trust, and support from the National Institute of Health and Care Research (NIHR) as NIHR Academic Clinical Fellow 2011 to 2013 and NIHR Academic Clinical Lecturer 2020 to 2024. She works at the National Hospital for Neurology and Neurosurgery, London.

RO is an author of a potentially eligible Cochrane Review update in development entitled "Antioxidant treatment for amyotrophic lateral sclerosis or motor neuron disease". He is a member of the Cochrane Neuromuscular editorial board but will play no part in the editorial process for this review. He is engaged in research and clinical activity as associate professor and consultant neurologist in ALS, (UCL),

University College London NHS Hospitals Foundation Trust, Royal Free London, East and North Hertfordshire NHS Trust and private practice.

NP has no known commercial conflicts of interest.

AAC works as a Consultant Neurologist specialising in ALS/MND at King's College Hospital (KCL), is Director of the King's MND Care and Research Centre, and is Co-lead for the NIHR Maudsley Biomedical Research Centre Neuropsychiatry and Psychosis theme. He is Executive Board Member of TRICALS, a not-for-profit organisation for trial delivery; Programme Board Chair for the International Alliance of ALS/MND Associations; and Scientific Advisory Board member of AMG Healey Center Massachusetts General Hospital. He declares the following payments from commercial organisations:

- Payments to institution (with personal benefit or control/access to funds) from:
  - Amylyx Pharmaceuticals (trial interpretation and design, Principal Investigator (PI));
  - Apellis (consultancy, PI and Chief Investigator (CI));
  - Biogen Idec (consultancy, educational roles, PI, scientific advisory boards, mutation adjudication);
  - Brainstorm Therapeutics (consultancy);
  - Cytokinetics Inc (consultancy, educational roles, PI, CI, scientific advisory boards, mutation adjudication);
  - Eli Lilly and Company (consultancy, educational roles);
  - GlaxoSmithKline (consultancy, educational roles);
  - Mitsubishi Tanabe Pharma Corporation (consultancy, PI, trial design, collaborative research on clinical staging);
  - Novartis Gene Therapies, Inc. (formerly known as AveXis Inc) (consultancy related to ALS);
  - Orion Corporation (clinical trial design, scientific advisory board, PI, CI);
  - Quralis (consultancy, scientific advisory board, CI, PI);
  - WaVe (consultancy, trial design, scientific advisory board, PI).
- Oxford University Press: annual stipend and travel costs as Deputy Editor of *Brain* (Oxford University Press).
- Book royalties: *The Beginner's Guide to the Brain* (Oneworld Publications) and *Complex Disease Genetics: a Laboratory Manual* (Cold Spring Harbor Laboratory Press).
- Private ALS/MND practice via KCL.

He has published opinions relevant to the interventions in the work: an opinion piece on genetics in ALS/MND (*Nature*), an editorial on gene therapy in ALS/MND (*New England Journal of Medicine*), appearance on BBC Breakfast TV talking about ALS/MND and its treatment (BBC), discussion panels on ALS/MND treatment (ALS Association, USA), various recorded talks, patient-research forums and presentations on YouTube, and published reviews on ALS/MND (*Lancet*, *Lancet Neurology*, *Nature Reviews Neurology*, *Nature Reviews Neuroscience*, *New England Journal of Medicine*). A signatory on the ENCALS declaration for Edaravone (www.encals.eu/wp-content/uploads/2017/08/ENCALS-statement-on-edaravone-FINAL.pdf).

Affiliations/relationships with organisations with a declared opinion or position on clinical trials in ALS (all agree they should be taking place and accelerated in ALS): ENCALS, TRICALS, NINDS/NIH, NIHR, MND Association, ALS Association, My Name'5 Doddie Foundation, MND Scotland, ALS Canada and the International Alliance of ALS/MND Associations.

Involvement in studies relevant to the topic of the review (with funding source(s)):

- OrionPharma: Cudkowicz 2021; Al-Chalabi 2019a; Al-Chalabi 2019b.
- Cytokinetics Inc: Shefner 2016; Shefner 2019.
- Medical Research Council (MRC) through EU Joint Programme – Neurodegenerative Disease Research (JPND): Fang 2018.
- Biogen: Cudkowicz 2013.
- European Commission Horizon 2020: Camu 2020.
- European Commission FP7: Al-Chalabi 2011; Giovannelli 2021; Lenglet 2014; UKMND-LiCALS Study Group 2013.
- Fight MND; MND Research Institute of Australia; MND Association of England, Wales and Northern Ireland; GSK; supply of Triumeq by ViiV Healthcare: Gold 2019.
- MND Association: van Eijk 2017.
- Reanalysis of a commercial clinical trial from Mitsubishi Tanabe Pharma using King's Clinical Staging – the original study was funded by Mitsubishi Tanabe Pharma; the reanalysis was not funded but was a collaboration: Al-Chalabi 2021.

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- Various, UK

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External sources

- NIHR, MNDA, UK

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