FORE FRONT

Cutting edge research into Frontotemporal Dementia and Motor Neurodegenerative Syndromes

MND/ALS: Thepaeutic Options

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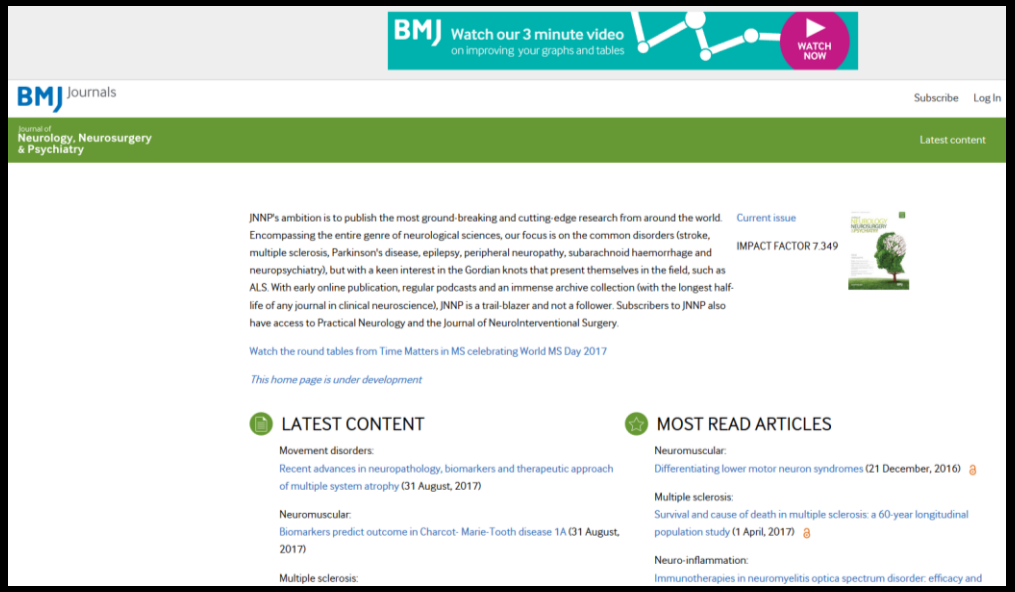
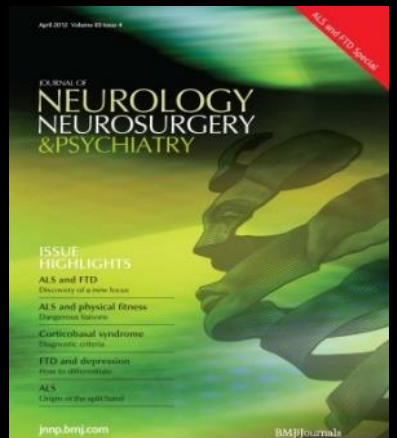
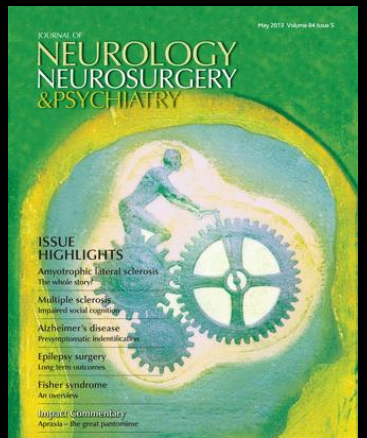
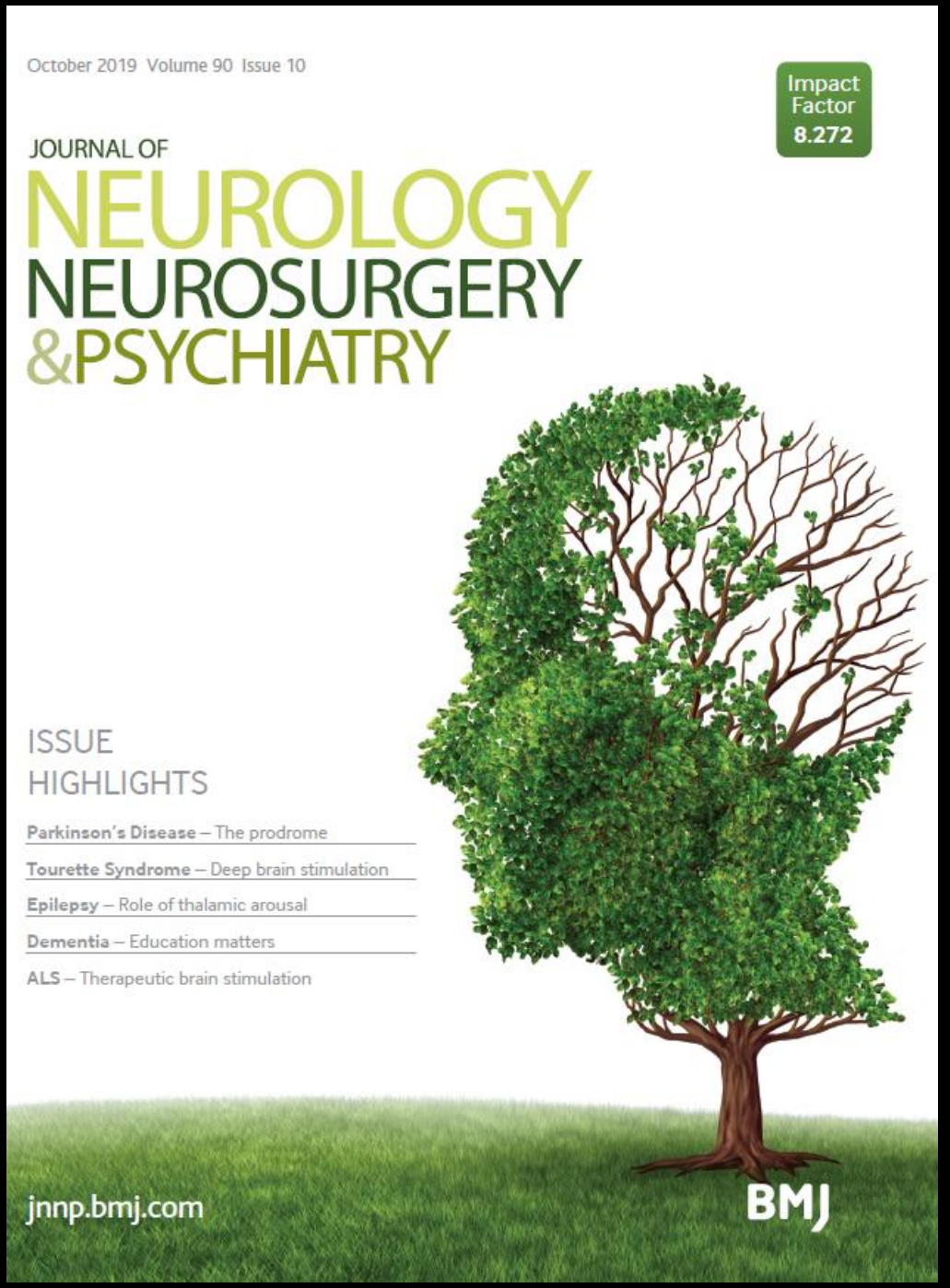
Disclosures



http://jnnp.bmj.com







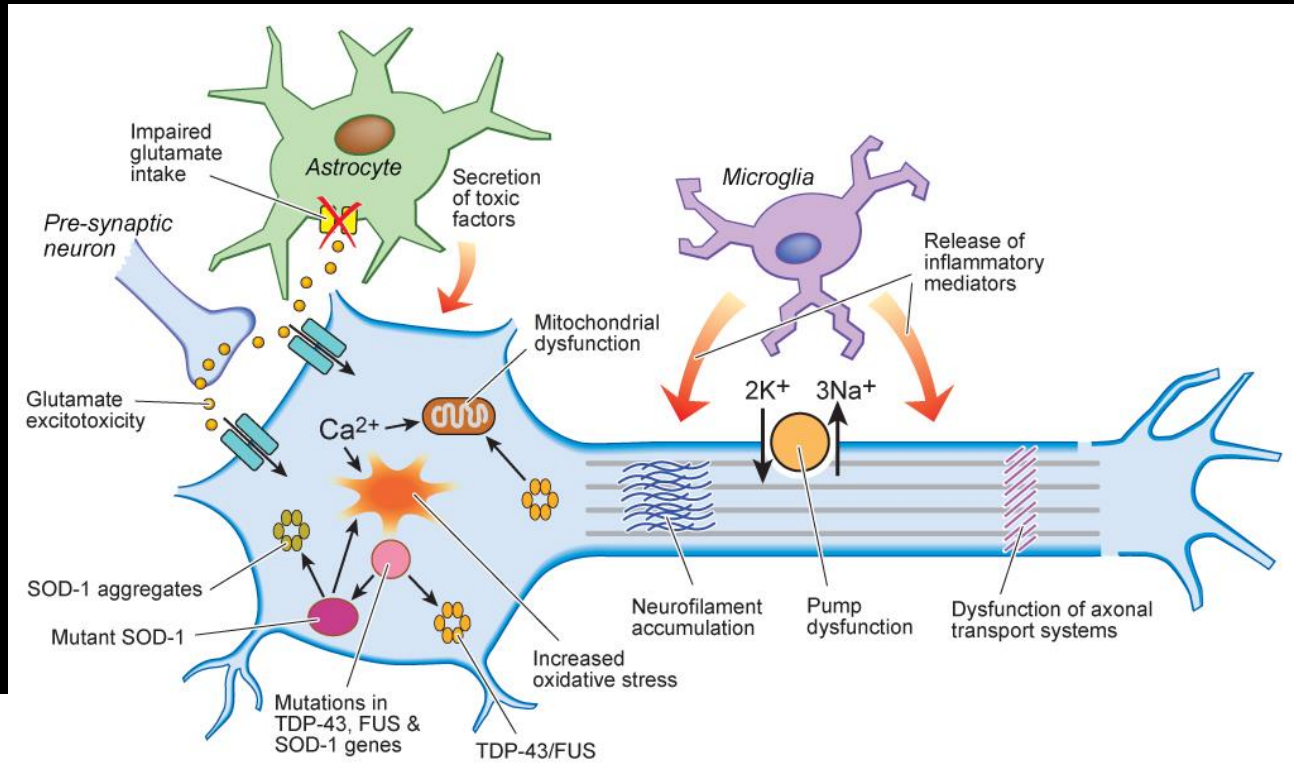
Learning Objectives:

1. Multidisciplinary Care
2. Disease modifying therapy
3. New Horizons

Key Message:
The therapeutic landscape is transforming

Treatment - beginnings:

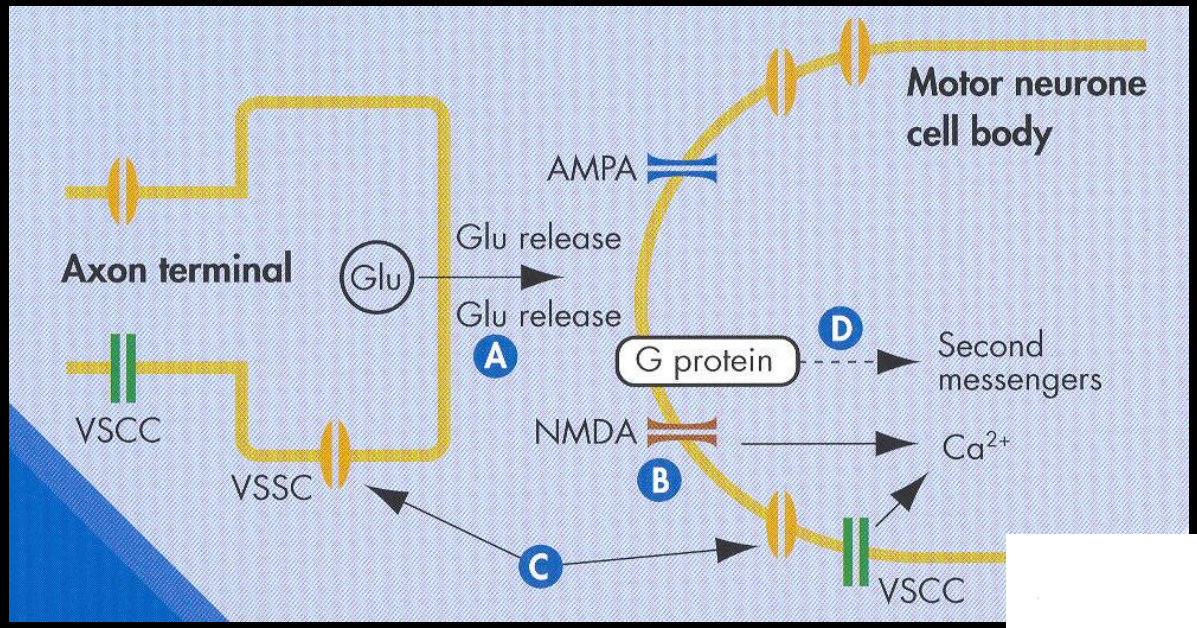
- 1993: Glutamate toxicity mediated via redox system
- ↑ CSF glutamate
- 'excitotoxicity' theory



Amyotrophic lateral sclerosis

Matthew C Kiernan, Steve Vucic, Benjamin C Cheah, Martin R Turner, Andrew Eisen, Orla Hardiman, James R Burrell, Margaret C Zoing

The Lancet 2011



The New England
Journal of Medicine

Volume 330 MARCH 3, 1994 Number

A CONTROLLED TRIAL OF RILUZOLE IN AMYOTROPHIC LATERAL SCLEROSIS

G. Bensimon, L. Lacomblez, V. Meininger, and the ALS/Riluzole Study Group*

RP 54274 – 420 :

1. International clinical trials
2. Early access to Riluzole
3. Expand the safety profile

Clinical study

Riluzole therapy for motor neurone disease: An early Australian experience (1996–2002)

Margie C. Zoing [a], David Burke [b], Roger Pamphlett [c], Matthew C. Kiernan [a,d,*]

[a] Multidisciplinary Motor Neurone Disease Service, Institute of Neurological Sciences, Prince of Wales Hospital, Sydney, New South Wales, Australia
[b] Institute of Clinical Neurosciences, University of Sydney and Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
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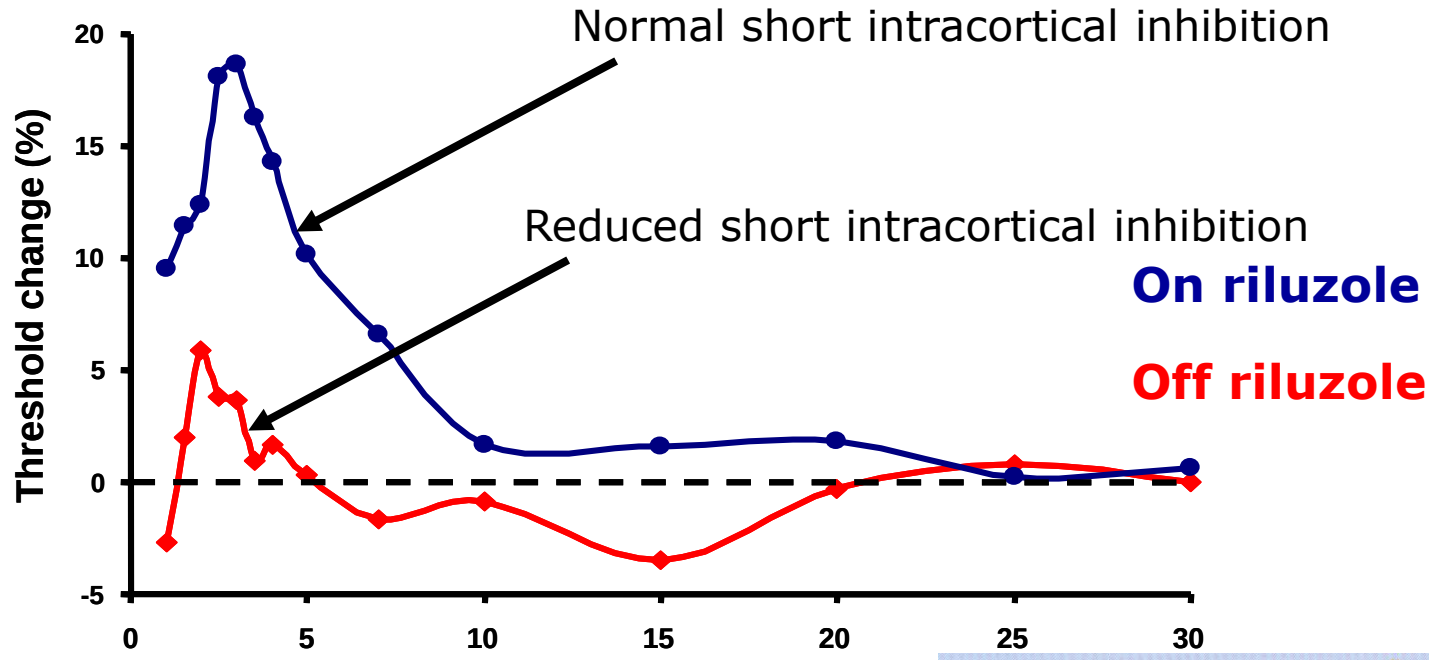
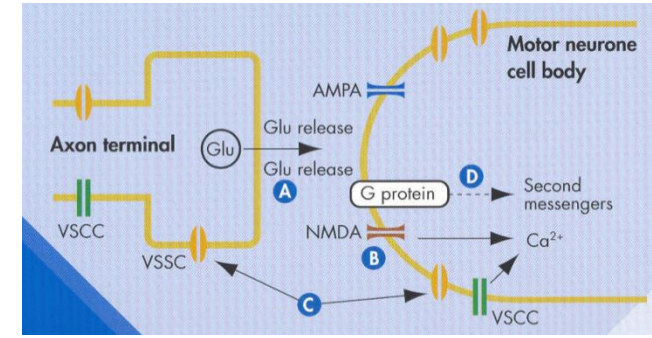
Threshold Tracking TMS



doi:10.1093/brain/awt085 Brain 2013: 136; 1361–1370 | 1361
BRAIN
A JOURNAL OF NEUROLOGY

Riluzole exerts central and peripheral modulating effects in amyotrophic lateral sclerosis

Steve Vucic,[1,2] Cindy Shin-Yi Lin,[2,3] Benjamin C. Cheah,[2] Jenna Murray,[2] Parvathi Menon,[1] Arun V. Krishnan[2,3] and Matthew C. Kiernan[2,4]



Riluzole – how and when?

Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study

Ton Fang, Ahmad Al Khleifat, Jacques-Henri Meurgey, Ashley Jones, P Nigel Leigh, Gilbert Bensimon, Ammar Al-Chalabi

Lancet Neurol 2018; 17: 416–22
Published Online
March 7, 2018
http://dx.doi.org/10.1016/
S1474-4422(18)30054-1

See Comment page 385

Summary

Background Riluzole is the only drug to prolong survival for amyotrophic lateral sclerosis (ALS) and, at a dose of 100 mg, was associated with a 35% reduction in mortality in a clinical trial. A key question is whether the survival benefit occurs at an early stage of disease, late stage, or is spread throughout the course of the disease. To address this question, we used the King's clinical staging system to do a retrospective analysis of data from the original dose-ranging clinical trial of riluzole.

Comment

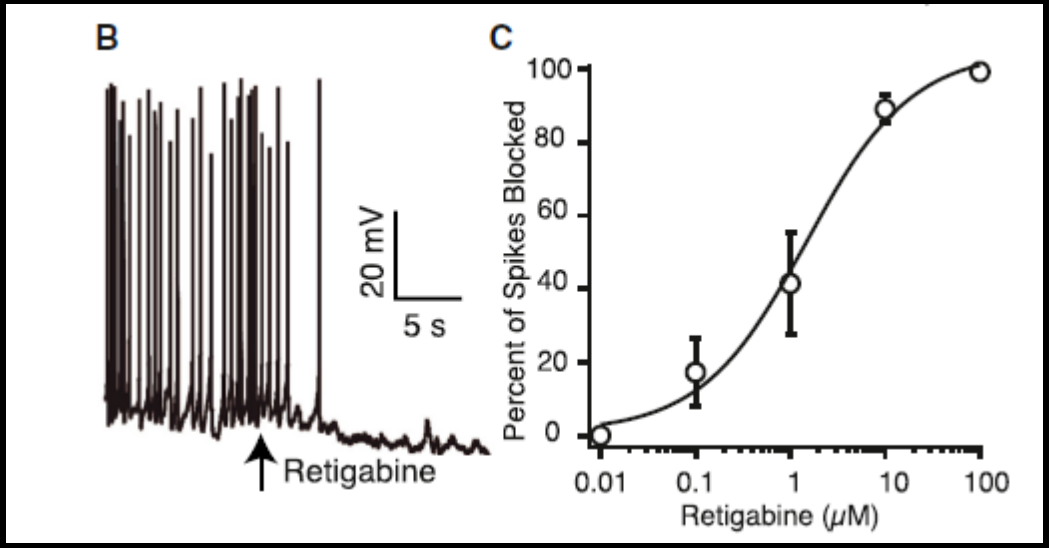
Riluzole, disease stage and survival in ALS

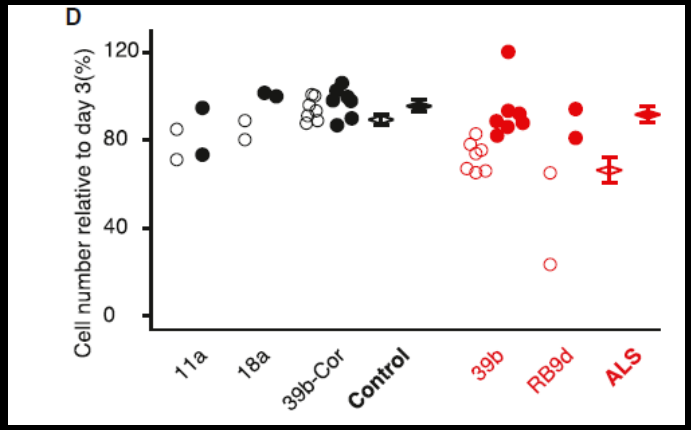
Lancet Neurol 2018
Published Online
March 7, 2018
http://dx.doi.org/10.1016/

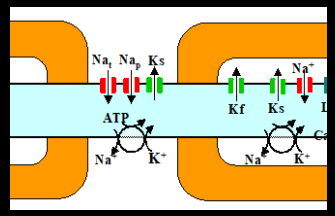
Following pivotal clinical trials in amyotrophic lateral sclerosis (ALS), approval of riluzole by the US Food and Drug Administration in 1995 was met with optimism. The argument for earlier efficacy might seem more conceptually feasible than later effects, given the lower likelihood that any treatment could confer a significant

Intrinsic Membrane Hyperexcitability of Amyotrophic Lateral Sclerosis Patient-Derived Motor Neurons

Brian J. Wainger,[1,2,8] Evangelos Kiskinis,[3,8] Cassidy Mellin,[1] Ole Wiskow,[3] Steve S.W. Han,[3,4] Jackson Sandoe,[3] Numa P. Perez,[1] Luis A. Williams,[3] Seungkyu Lee,[1] Gabriella Boulting,[3] James D. Berry,[4] Robert H. Brown, Jr.,[5] Merit E. Cudkowicz,[4] Bruce P. Bean,[6] Kevin Eggan,[3,4,7,*] and Clifford J. Woolf[1,6,*]







NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

A Phase 2 Pharmacodynamic Trial of Ezogabine on Neuronal Excitability in Amyotrophic Lateral Sclerosis

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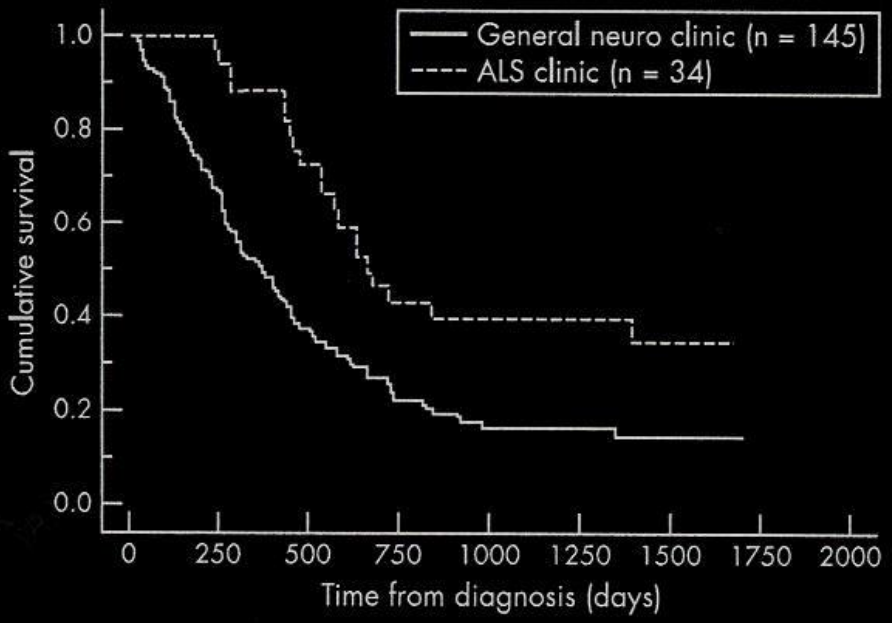
MND

Multidisciplinary



PAPER

Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000

B J Traynor, M Alexander, B Corr, E Frost, O Hardiman

J Neurol Neurosurg Psychiatry 2003;**74**:1258–1261

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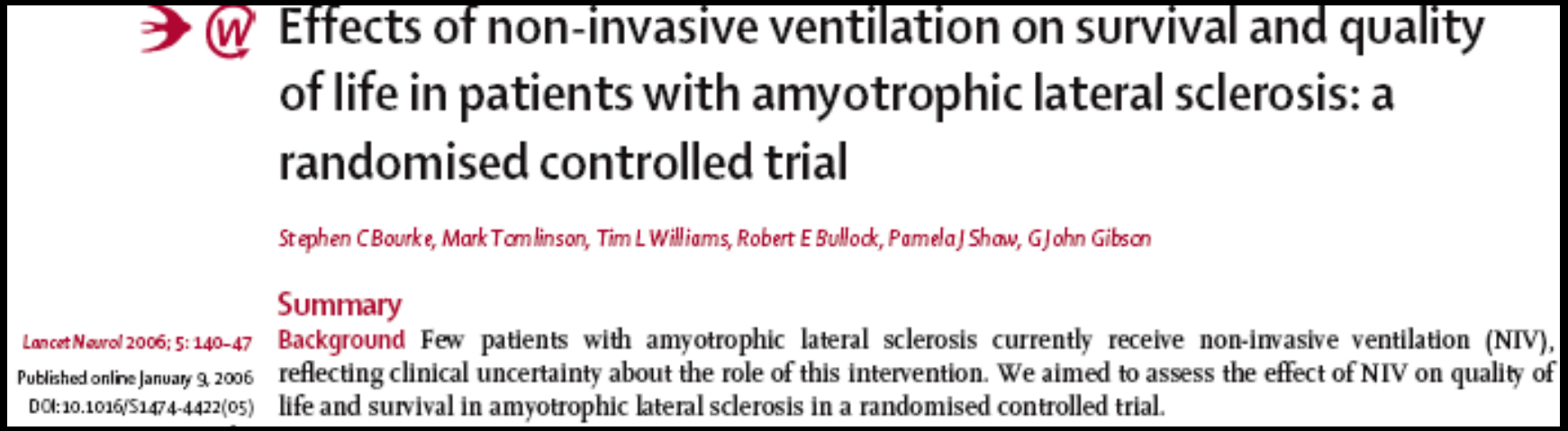
Respiratory support



Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial

Stephen C Bourke, Mark Tomlinson, Tim L Williams, Robert E Bullock, Pamela J Shaw, G John Gibson

Lancet Neurol 2006; 5: 140–47
Published online January 9, 2006
DOI:10.1016/S1474-4422(05)

Summary

Background Few patients with amyotrophic lateral sclerosis currently receive non-invasive ventilation (NIV), reflecting clinical uncertainty about the role of this intervention. We aimed to assess the effect of NIV on quality of life and survival in amyotrophic lateral sclerosis in a randomised controlled trial.

- NIV compared to standard care
- Improved survival
- Maintenance or improved quality of life
- Unresolved – when to institute?

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Exercise Therapy: Sydney Hydrotherapy Study

- Goals – relaxation, strength & mobility
- 80% reported improved function out of the water
- Mood impact 60%; ↑ QoL; ‘makes me happier’
- 80% achieved goals; keep coming!
- None experienced difficulties

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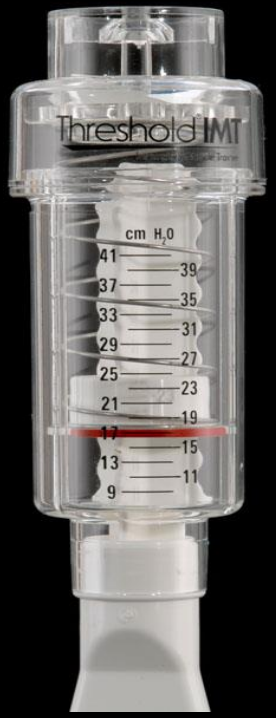
Inspiratory Muscle Training



- INSPIRATionAL
  (**Inspira**tory **T**raining for **A**myotrophic **L**ateral Sclerosis

- Threshold IMT
- Commence training at 2nd visit
- 12 weeks
- 10 minutes 3x/day
- Threshold load is gradually increased over time
- Strengthened respiratory muscles
- 2 INSPIRATionAL underway

ORIGINAL ARTICLE

INSPIRATIonAL – INSPIRAtory muscle Training In Amyotrophic Lateral sclerosis

BENJAMIN C. CHEAH[1,2], ROBERT A. BOLAND[1], NINA E. BRODATY[2], MARGIE C. ZOING[1,2], SANDRA E. JEFFERY[2], DAVID K. MCKENZIE[1,2] & MATTHEW C. KIERNAN[1,2]

[1]*Prince of Wales Medical Research Institute & Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, and* [2]*Multi-Disciplinary ALS Clinical Service, Prince of Wales Hospital, Sydney, New South Wales, Australia*

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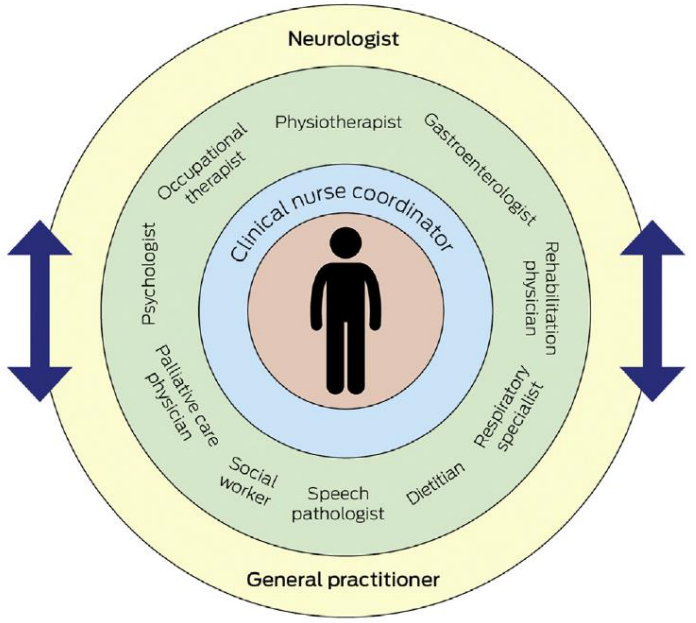
Symptomatic therapies

- Muscle cramps
- Spasticity
- Sialorrhea
- Dyspnea
- Weight loss; dysphagia
- Emotional lability

2 Motor neurone disease management: multidisciplinary care model



The multidisciplinary care model centres on the patient with motor neurone disease. It involves dynamic integration of medical, nursing and allied health professionals for optimal patient management. Care is often coordinated by the clinical nurse, with the neurologist and general practitioner overseeing all aspects of care. ◆

Motor neurone disease: progress and challenges

Thanuja Dharmadasa[1], Robert D Henderson[2], Paul S Talman[3], Richard AL Macdonell[4], Susan Mathers[5], David W Schultz[6], Merrillee Needham[7], Margaret Zoing[1], Steve Vucic[8], Matthew C Kiernan[1]

Current Clinical Trials

Research

JAMA Neurology | Original Investigation

Association of Regulatory T-Cell Expansion With Progression of Amyotrophic Lateral Sclerosis

A Study of Humans and a Transgenic Mouse Model

Rebecca K. Sheean, PhD; Fiona C. McKay, PhD; Erika Cretney, PhD; Christopher R. Bye, PhD; Nirma D. Perera, PhD; Doris Tomas, BSc; Richard A. Weston, MB, ChB; Karlene J. Scheller, PhD; Elvan Djouma, PhD; Parvathi Menon, PhD; Stephen D. Schibeci, MSc; Najwa Marmash, BSc; Justin J. Yerbury, PhD; Stephen L. Nutt, PhD; David R. Booth, PhD; Graeme J. Stewart, MD; Mathew C. Kiernan, DSc; Steve Vucic, PhD; Bradley J. Turner, PhD

IMPORTANCE Neuroinflammation appears to be a key modulator of disease progression in amyotrophic lateral sclerosis (ALS) and thereby a promising therapeutic target. The CD4⁺Foxp3⁺ regulatory T-cells (Tregs) infiltrating into the central nervous system suppress neuroinflammation and promote the activation of neuroprotective microglia in mouse models of ALS. To our knowledge, the therapeutic association of host Treg expansion with ALS progression has not been studied in vivo.

Editorial

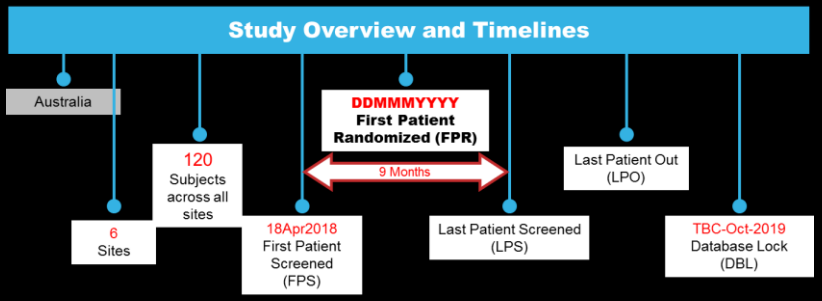
Supplemental content

EDITORIAL

The Role of Regulatory T Lymphocytes in Amyotrophic Lateral Sclerosis

David R. Beers, PhD; Weihua Zhao, MD, PhD; Stanley H. Appel, MD

Phase 2 Randomised Placebo-Controlled Double-Blind Study to Assess the Efficacy and Safety of Tecfidera in Patients with Amyotrophic Lateral Sclerosis –TEALS Study



ALS – new horizons

- Masitinib – tyrosine kinase inhibitor

Paris, 20 March 2017, 8am

AB Science announces positive top-line results of final analysis from study AB10015 of masitinib in amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease

Primary analysis is a success and confirms interim analysis

Company to host webcast on masitinib in ALS

AB Science SA (NYSE Euronext - FR0010557264 - AB), a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), today announced that the phase 2/3 study AB10015 of masitinib in amyotrophic lateral sclerosis (ALS) has met its pre-specified primary endpoint. This is the first successful phase 3 trial of a tyrosine kinase inhibitor in the treatment of ALS, signifying masitinib as first-in-class for ALS, with a unique mechanism of action against microglia cells.

- AB14008 – contacted to incorporate global sites

ALS – new horizons

- Edaravone (Mitsubishi Pharma) – free radical scavenger
  - Phase 3; younger onset, FVC >80%
  - Recent FDA approval

3.5. *Edaravone, a free radical scavenger*

Edaravone was developed as a free radical scavenger that has been used to treat patients with acute cerebral infarction in Japan, in addition to several other neurological diseases [82–84]. Edaravone appears to remove lipid peroxides and hydroxyl radicals during cerebral ischemia and protects neurons

EXPERT REVIEW OF NEUROTHERAPEUTICS, 2016
http://dx.doi.org/10.1080/14737175.2016.1197774

Taylor & Francis
Taylor & Francis Group

REVIEW

Novel therapies in development that inhibit motor neuron hyperexcitability in amyotrophic lateral sclerosis

Yu-ichi Noto[a], Kazumoto Shibuya[a], Steve Vucic[b] and Matthew C. Kiernan[a]

[a]Brain and Mind Centre and Sydney Medical School, University of Sydney, Sydney, Australia; [b]Westmead Clinical School, University of Sydney, Sydney, Australia

ALS – promising studies

- Cytokinetics CK 2017357 Fortitude
- Mexilitene/Flecainide/membrane stabilizers
- Neural Stem and Brainstorm; ?gene therapy

NEALS consortium: The network of clinical sites and patients exist, so trials can be done well throughout the US, Canada, Europe and Australia.
And there is a growing pipeline of therapeutic targets and agents under development for ALS.

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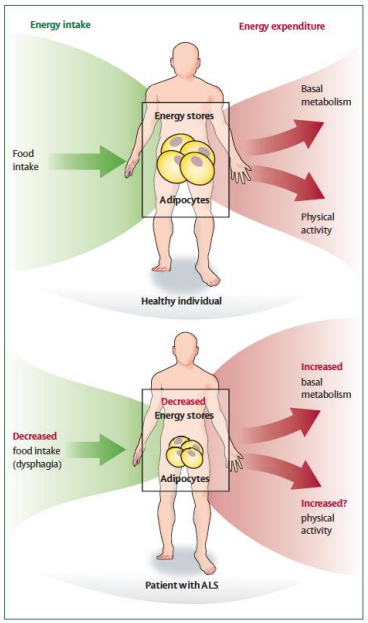
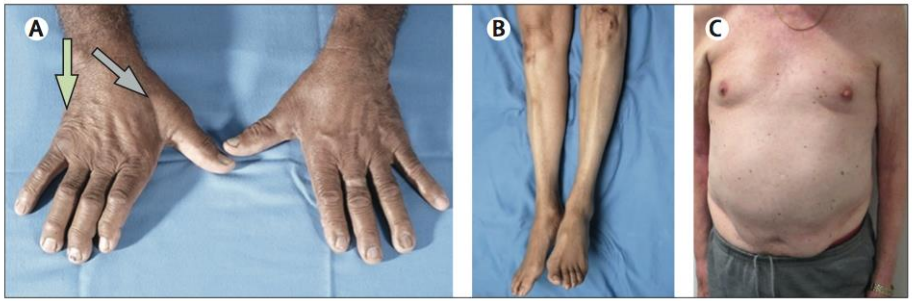
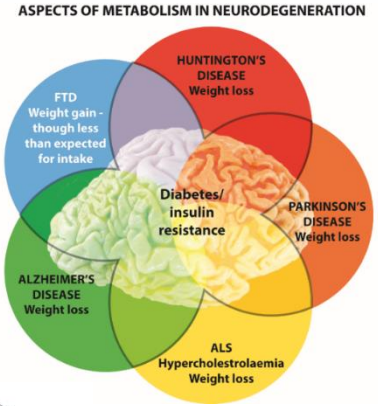
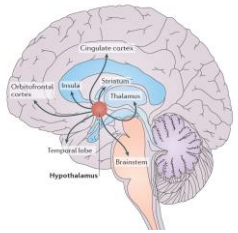
ALS, physiology & metabolism







- Hypermetabolism
- Hyperlipidemia
- Insulin resistance
- Low BMI: Higher BMI - prognosis
- **Eating behaviour and surviv**



REVIEWS

Amyotrophic lateral sclerosis and frontotemporal dementia: distinct and overlapping changes in eating behaviour and metabolism

Rebekah M Ahmed, Muireann Irish, Olivier Piguet, Glenda M Halliday, Lars M Ittner, Sadaf Farooqi, John R Hodges, Matthew C Kiernan

Physiological changes in neurodegeneration — mechanistic insights and clinical utility

Rebekah M. Ahmed[1,2*], Yazi D. Ke[3], Steve Vucic[1], Lars M. Ittner[3,4,5], William Seeley[6], John R. Hodges[1,7], Olivier Piguet[7,8], Glenda Halliday[1] and Matthew C. Kiernan[1,2]

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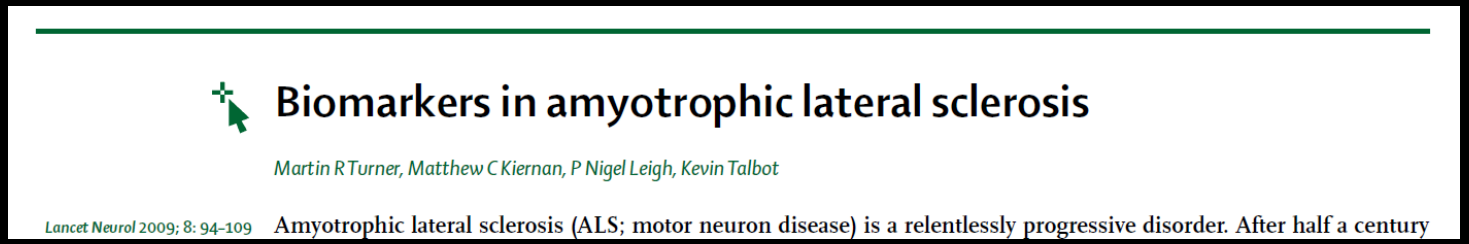
ALS – problems with designing trials

- Biomarkers



Biomarkers in amyotrophic lateral sclerosis

Martin R Turner, Matthew C Kiernan, P Nigel Leigh, Kevin Talbot

Lancet Neurol 2009; 8: 94–109

Amyotrophic lateral sclerosis (ALS; motor neuron disease) is a relentlessly progressive disorder. After half a century

- Clinical heterogeneity
- genotype/phenotype
- Phase 2 – unlikely to predict effect size
- Natural History

Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial

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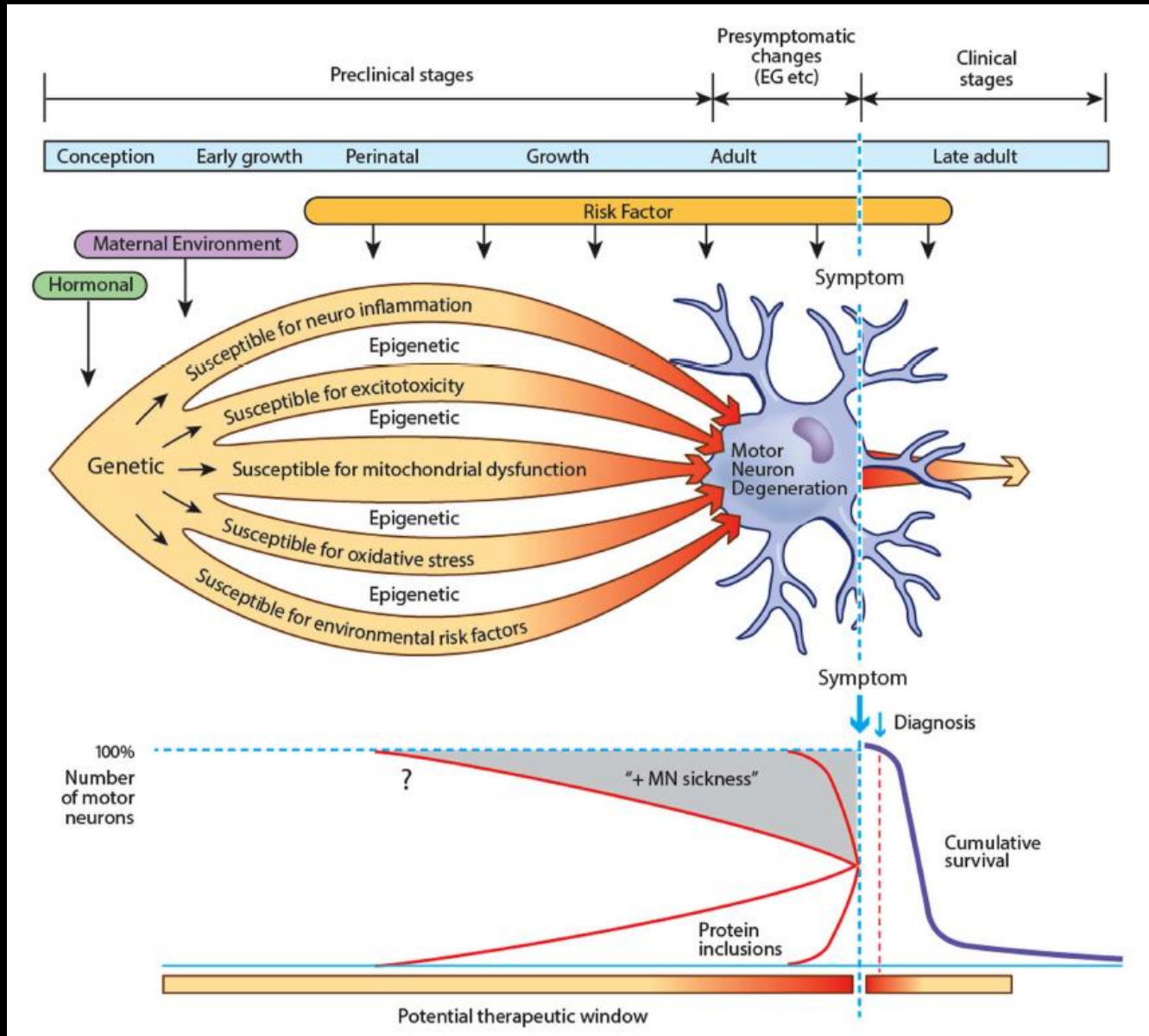
MND the future: when did it begin?

REVIEW

Amyotrophic lateral sclerosis: a long preclinical period?

Andrew Eisen,[1] Matthew Kiernan,[2] Hiroshi Mitsumoto,[3] Michael Swash[4,5]

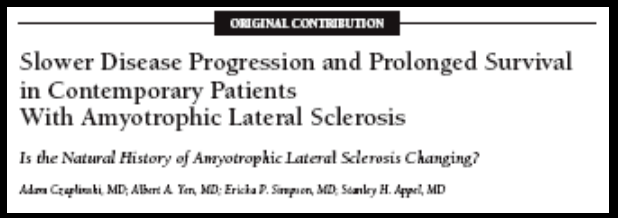


ALS – future approaches

- If ALS truly focal → regional therapy to contain spread

Conclusions

- Understanding of MND is evolving
- New therapeutic interventions in a multi-disciplinary care setting
- New diagnostic approaches → earlier Rx, more likely success
- Neuronal spread?
- Better outcomes



ORIGINAL CONTRIBUTION

Slower Disease Progression and Prolonged Survival in Contemporary Patients With Amyotrophic Lateral Sclerosis

Is the Natural History of Amyotrophic Lateral Sclerosis Changing?

Adam Czaplinski, MD; Albert A. Yen, MD; Ericka P. Simpson, MD; Stanley H. Appel, MD

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MND – References

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Berlowitz DJ, Howard ME, Fiore JF, et al. Identifying who will benefit from non-invasive ventilation in amyotrophic lateral sclerosis/motor neurone disease in a clinical cohort. J Neurol Neurosurg Psychiatry 2016; 87: 280-286.

Murray L, Butow PN, White K et al. Advance care planning in motor neuron disease: A qualitative study of caregiver perspectives. Palliative Medicine 2016; 30(5): 471-478.

Burrell JR, Halliday GM, Kril JJ, et al. The frontotemporal dementia-motor neuron disease continuum. Lancet 2016; pii: S0140-6736(16)00737-746.