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ACNR

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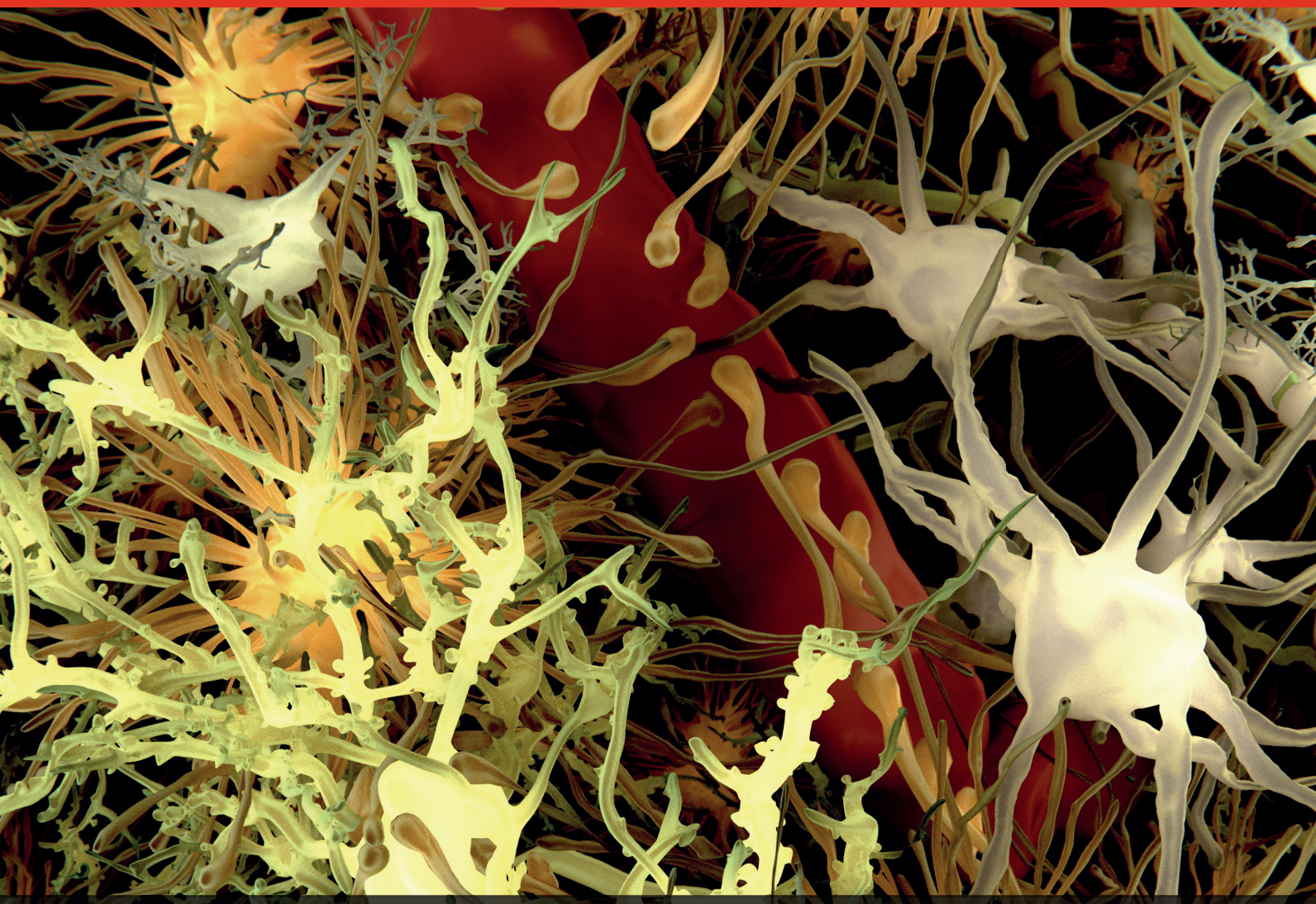
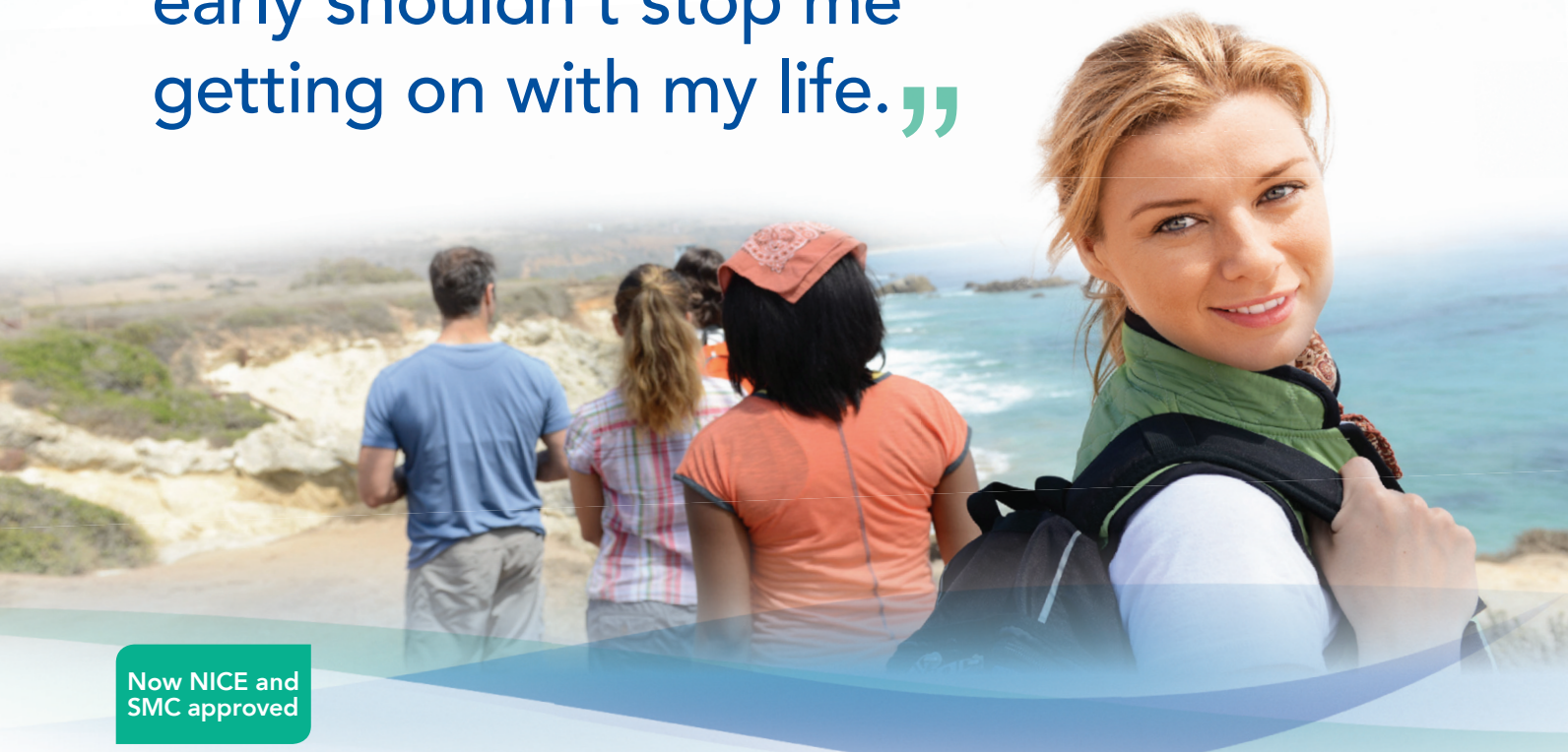
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

“Starting my MS treatment early shouldn’t stop me getting on with my life.”



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Abbreviated Prescribing Information. AUBAGIO▼14 mg film-coated tablets. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **PRODUCT COMPOSITION:** Each film-coated tablet contains 14 mg of teriflunomide. **INDICATIONS:** AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). **DOSAGE AND ADMINISTRATION:** The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. The recommended dose of teriflunomide is 14 mg once daily. The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. 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Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **EDUCATIONAL GUIDANCE**: Prior to prescribing AUBAGIO, physicians must familiarise themselves with educational materials which consist of a *Healthcare Professional Education/Discussion guide* and they should provide their patients with a *Patient Card* and *Patient Leaflet*. **WARNINGS AND PRECAUTIONS:** ***Monitoring***: *Before starting treatment* the following should be assessed: blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Exclude pregnancy. *During treatment* the following should be monitored: blood pressure, ALT/SGPT. A CBC should be performed based on signs and symptoms. ***Accelerated elimination procedure:*** Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide. (For further information, please refer to the SmPC). ***Hepatic effects:*** Assess liver enzymes before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected and discontinuation should be considered if liver enzymes are confirmed as >3x ULN. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease. AUBAGIO should be used with caution in patients who consume substantial quantities of alcohol. ***Blood pressure***: Must be checked before the start of teriflunomide treatment and periodically thereafter. ***Infections:*** Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with teriflunomide. ***Haematological effects***: A mean decrease of less than 15% from baseline affecting white blood cell counts have been observed. Obtain complete blood count with differential prior to initiation of treatment, thereafter CBC should be assessed as indicated by clinical signs and symptoms. In patients with pre-existing cytopenias there might be a higher risk of haematological disorders with teriflunomide. In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the accelerated elimination procedure be considered. ***Respiratory reactions***: Due to the potential risk of interstitial lung disease, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. ***Skin reactions:*** In case of ulcerative stomatitis, or if skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. ***Immunosuppressive/Immunomodulating therapies:*** Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. ***Peripheral neuropathy***: Confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure. ***Vaccination***: Live attenuated vaccines should be avoided. **SWITCHING to or from AUBAGIO**: No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. **CONCOMITANT USE AND DRUG INTERACTION:** Co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. Rifampicin and other known potent CYP and transporter inducers, medicinal products metabolised by CYP2C8, oral contraceptives, medicinal products metabolised by CYP1A2, OAT3 substrates, BCRP substrates and OATP substrates should be used with caution during treatment with teriflunomide. For patients receiving teriflunomide treatment with cholestyramine or activated charcoal is not recommended. For co-administration of warfarin with teriflunomide, close INR follow-up and monitoring is recommended. **PREGNANCY AND LACTATION:** ***Pregnancy:*** Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. In case of suspicion of pregnancy, patient must notify the physician. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the accelerated elimination procedure. In women wishing to become pregnant, teriflunomide should be stopped and an accelerated elimination procedure is recommended (Please refer to the SmPC for further information). Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens during the accelerated elimination procedure. Use of alternative contraceptive methods is recommended. ***Lactation***: Breast-feeding women must not receive teriflunomide. **UNDESIRABLE EFFECTS:** Based on placebo-controlled studies the most commonly reported adverse reactions in the teriflunomide treated patients were: influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia. ***Very common (≥ 1/10)*** Influenza, upper respiratory tract infection, urinary tract infection, paresthesia, diarrhoea, nausea, alopecia, ALT increase. ***Common (≥ 1/100 to < 1/10);*** Bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, mild allergic reactions, anxiety, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, hypertension, vomiting, toothache, rash, acne, musculoskeletal pain, myalgia, pollakiuria, menorrhagia, pain, GGT increase, AST increase, weight decrease, neutrophil count decrease, WBC decrease, post-traumatic pain. For listings and further information on adverse reactions, please refer to the SmPC. **Legal Classification:** POM (Prescription Only Medicine). **List Price:** £1037.84 per 28 day pack. **MARKETING AUTHORISATION NUMBER:** EU/1/13/838/001-005. **MARKETING AUTHORISATION HOLDER:** Sanofi-Aventis Groupe. 54, Rue La Boétie. F-75008 Paris. France. **FULL PRESCRIBING INFORMATION AVAILABLE FROM** Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford OX4 2SU. **DATE OF PREPARATION:** October 2013.

▼AUBAGIO is subject to additional monitoring. This will allow quick identification of new safety information. Adverse Events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard Adverse events should also be reported to Genzyme Tel: 01865 405 200

References: 1. AUBAGIO (teriflunomide) Summary of Product Characteristics. November 2013. **2.** Confavreux C, O'Connor P, Comi G et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* January 2014 [Published online]. DOI: 10.1016/ S1474-4422(13)70308-9. **3.** O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011; 365(14): 1293-1303. **4.** Confavreux C, Li DK, Freedman MS, et al. Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler. 2012 Sep; 18(9): 1278-89.

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PUBLISHER AND ADVERTISING Rachael Hansford
T. 01747 860168 M. 07989 470278 E. rachael@acnr.co.uk

EDITORIAL John Gustar E. editorial@acnr.co.uk

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Editorial board and contributors

Mike Zandi is Editor of ACNR, Senior Clinical Research Associate in the Department of Clinical Neurosciences, University of Cambridge, and Honorary Consultant Neurologist at Addenbrooke's Hospital and Cambridgeshire and Peterborough NHS Foundation Trust. He is working on psychiatric presentations of autoimmune encephalitis, and the development of clinical trials and biomarkers for NMDAR and other antibody-associated neuropsychiatric disorders.

Todd Hardy is Associate Editor of ACNR. He is a Neurologist at Concord Hospital and Clinical Senior Lecturer in Neurology at the University of Sydney, Australia. He is interested in multiple sclerosis and other neuroinflammatory disorders.

Andrew Bateman is ACNR's Rehabilitation Editor. He is Clinical Lead for NeuroRehab in Cambridgeshire Community Services NHS Trust and Affiliated Lecturer in Dept of Psychiatry at University of Cambridge. He is Head of Department at the Oliver Zangwill Centre for Neuropsychological Rehabilitation, where alongside clinical work he has led research & educational activity.

Boyd Ghosh is the Editor of our Conference News section. He is currently a Specialist Registrar in Southampton having completed a PhD in Cambridge in cognitive neuroscience. His special interests are cognition and movement disorders, with a particular interest in progressive supranuclear palsy.

Imran Noorani is Assistant Conference News Editor. He is an Academic Neurosurgery Foundation Trainee in Southampton General Hospital having trained in Cambridge. His academic interest is oculomotor neurophysiology, specifically models of saccadic decision and their potential application to neurological disorders.

Rhys Davies is Editor of our Book Review Section. He is a consultant neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.

Gemma Cummins is ACNR's Journal Reviews editor. Gemma is a Specialist registrar in Neurology at Addenbrooke's Hospital, Cambridge and is currently completing a PhD on movement disorders and cognition at the Van Geest Centre for Brain Repair, Cambridge.

Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Stevan Wing is the Web and Digital Editor of ACNR and a Specialist Neurology Registrar at Addenbrooke's Hospital. He works on dementia and movement disorders at the University of Cambridge.

Roger Barker is Consulting Editor of ACNR, Professor of Clinical Neuroscience at the University of Cambridge and an Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson's and Huntington's disease.

Alasdair Coles is Consulting Editor of ACNR. He is a University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Mike Zandi, Editor.

The success of clinical trials of disease modifying therapies in neurodegenerative disorders will be greatly helped by validated biomarkers to identify early disease and track disease progression. This has been the priority of several research groups and will reduce the cost and patient numbers needed to generate a meaningful and significant outcome. But the data available and conventional models are limited. In this issue Alexandra Young, Neil Oxtoby, Jonathan Schott and Daniel Alexander from UCL introduce us to data-driven models in neurodegenerative disease, and highlight three statistical techniques which have performed best. One therapeutic approach for degenerative disease is foetal cell transplantation. Anne Rosser and Stephen Dunnett from Cardiff write an update on striatal cell transplants in Huntington's Disease in an excellent brief and clear review with many insights from transplants done to date. Lilia Dimitrov and Ben Turner conclude their timely round up of the current state of play of oral therapies for multiple sclerosis, by focussing on di-methyl fumarate in this issue. This is a rapidly changing landscape, and the authors note a recent case of PML with the drug. The ECTRIMS/ACTRIMS conference is reviewed by Alasdair Coles on page 25.

In the rest of the journal, David Menassa and Katarzyna Bera from Oxford and Bristol write a short neuroimmunological commentary on recent work on GABA(A) receptor autoimmunity. Tom Kelly (Newcastle) and Andrew Larner (Liverpool) write on the unexpected origins of culture-free neuropsychological testing in our historical article. Steve Vucic from Sydney provides a clear clinical update and primer on the varied phenotypes of motor neurone disease. In our rehabilitation article introduced by Andrew Bateman, vocational rehabilitation and story telling approaches in medical leadership projects are showcased. We are pleased to announce that Valerie Voon in Cambridge has joined us as our editor in Neuropsychiatry, and look forward to her contributions in 2015. We hope you enjoy this issue into the end of 2014.

Mike Zandi, Editor.
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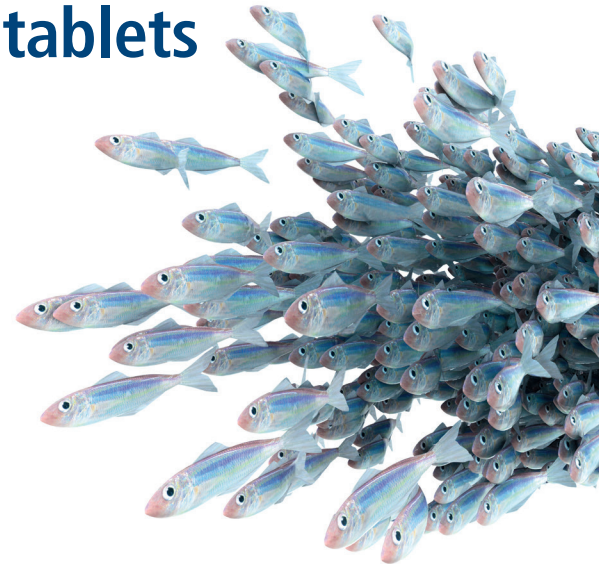

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Dose can be further increased if required by 250 mg twice daily every two weeks to a maximum of 1500 mg twice daily. *Adjunctive therapy:* Adults and adolescents (12 to 17 years) weighing ≥50 kg: Initial dose 500 mg twice daily. Dose can be increased, if necessary, up to 1500 mg twice daily. Dose changes made in 500 mg twice daily increases or decreases every two to four weeks. Take orally, swallowed with a sufficient quantity of liquid, with or without food. Daily dose in two equally divided doses. Elderly: Adjust dose in renal impairment. Renal impairment: Adjust dose according to renal function. Hepatic impairment: severe impairment reduce daily maintenance dose by 50% when CLcr <60 ml/min. Children: Prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. Coated granules not adapted for use in children under 6 years. Available dose strengths not appropriate for initial treatment in children weighing less than 25 kg or for doses below 250 mg. Monotherapy: No data in children and adolescents below 16 years. Adjunctive therapy: Infants from 6 months, children and adolescents weighing less than 50 kg: Oral solution preferred formulation in children under 6 years. Initial dose 10 mg/kg daily. Dose can be increased if required up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. Use lowest effective dose. Dose in children ≥50 kg same as adults. Infants from 1 month to <6 months: use oral solution. **Contraindications:** Hypersensitivity to levetiracetam, to other pyrrolidone derivatives or to any of the excipients. Infants and children under the age of 6 years (levetiracetam oral solution is the preferred formulation for use). **Special warnings and precautions for use:** Patients with renal or severe hepatic dysfunction may require dose adjustment. Discontinue gradually (see SmPC). Although available data in children do not suggest impact on growth and puberty, long term effects remain unknown. The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. Patients should be monitored for respective signs and appropriate treatment should be considered. **Effects on ability to drive and use machines:** Reaction time may be impaired. **Pregnancy/lactation:** A teratogenic risk cannot be completely excluded. Use during pregnancy, lactation and in women of childbearing potential without contraception is not recommended unless clearly necessary. Levetiracetam plasma levels decrease during pregnancy, particularly in the third trimester. **Side effects:** *Very common:* Nasopharyngitis, somnolence, headache. *Common:* convulsion, dizziness, vertigo, lethargy, tremor, impaired balance, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, anorexia (increased risk when coadministered with topiramate), rash, cough, asthenia/fatigue. *Uncommon:* thrombocyto-/leucopenia, weight increase or decrease, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional lability/mood swings, agitation, amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention, diplopia, blurred vision, abnormal liver function test, alopecia (in several cases recovery of hair loss was observed after discontinuation of levetiracetam), eczema, pruritus, muscular weakness, myalgia, injury. *Rare:* infection, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, pancreatitis, hepatic failure, hepatitis, neutro-, pancytopenia (bone marrow suppression identified in some of the cases), agranulocytosis, DRESS, hyponatraemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme. Side effects occurring more frequently than in other age groups: children and adolescents between 4 and 16 years: *Very common:* vomiting. *Common:* agitation, emotional lability, mood swings, aggression, abnormal behaviour, lethargy. Infants and children between 1 month and 4 years of age: *Very common:* irritability. *Common:* coordination abnormal. **Pack sizes and NHS price:** Packs of 60, 250 mg sachets £22.41 [PL14040/0029]; Packs of 60, 500 mg sachets £39.46 [PL14040/0030]; Packs of 60, 1000 mg sachets £76.27 [PL14040/0032]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany. **Prepared in:** June 2014. For further information on Desitrend® please contact Medical Information on MedInfo@desitin.co.uk.

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Adverse events should also be reported to Desitin Pharma Limited on MedInfo@desitin.co.uk.

UK/DD/14/0007 Date of preparation: August 2014.

Alexandra L Young

is studying for a PhD in Medical Imaging at University College London. She has a background in mathematics and computer science, which she applies to develop data-driven models of disease progression. Her main research focus is the development and application of the event-based model in sporadic Alzheimer's disease.

Neil P Oxtoby

has a quantum physics PhD from Griffith University (Brisbane, Australia). A brief stint in health informatics was followed by postdoctoral positions at the Universities of Hertfordshire (quantum information) and Liverpool (complex plasmas and object tracking). He now applies his mathematical, statistical, and state estimation skills to disease progression modelling.

Jonathan M Schott

is Reader in Clinical Neurology at University College London, and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square. He is interested in translational research in the dementias, with a particular focus on biomarkers for early diagnosis and disease tracking in Alzheimer's disease and related conditions, and how these can be employed as outcome measures for clinical trials particularly in the pre-symptomatic phase.

Daniel C Alexander

is Professor of Imaging Science in the Department of Computer Science and Centre for Medical Image Computing at University College London. His work focuses on computational modelling and optimisation for biomedical imaging and image analysis with a focus on application in Neurology and Oncology. He leads the Microstructure Imaging Group: mig.cs.ucl.ac.uk.

Correspondence to:
Alexandra Young,
Centre for Medical Image Computing,
Department of Computer Science,
University College London,
Gower Street, London WC1E 6BT
Email: alexandra.young.11@ucl.ac.uk

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Data-driven models of neurodegenerative disease

Summary

- Data-driven models provide a uniquely fine-grained multi-modal picture of disease progression.
- This offers major potential benefits to neurodegenerative disease research and clinical practice, by improving patient staging and monitoring, disease prognosis and differential diagnosis.
- To date these models have provided valuable insights into neurodegenerative disease progression patterns, particularly in Alzheimer's disease.
- Data-driven models are an emerging area of technology with numerous exciting opportunities for future developments.
- These techniques have wide potential further application to any disease or developmental process.

Neurodegenerative diseases are characterised by the temporal order and severity of a distinct set of symptoms and pathological changes that occur within the brain. Whilst the underlying mechanisms by which these pathologies arise and propagate are not fully understood, the development of imaging and CSF measures that reflect the presence and severity of these pathological changes is providing valuable insights, including opening a potential pre-symptomatic window where disease-modifying therapies may be most effective. Characterising the trajectories of these biomarkers over the time course of different neurodegenerative diseases is of great interest in order to build up a quantitative picture of disease progression.[1] Such a picture provides insight into the underlying disease biology and, moreover, provides a potential mechanism for patient staging and monitoring, disease prognosis and differential diagnosis.

Recently a range of hypothetical models have been proposed that describe the long-term progression of biomarkers associated with different neurodegenerative diseases, with a particular focus on Alzheimer's disease[1-3] (Figure 1). However, a fully quantitative data-driven model is required for practical application to patient staging and monitoring, prognosis and differential diagnosis. Wide recognition of the need for diverse multi-biomarker data sets to inform such quantitative progression models has lead to the establishment of large multi-centre biomarker studies including ADNI (sporadic Alzheimer's disease),[4] DIAN (familial Alzheimer's disease),[5] predict-HD (Huntington's disease),[6] PPMI (Parkinson's disease),[7] and many others. However, reconstructing biomarker trajectories from these data sets is challenging. The data are largely cross-sectional or with only a few years of follow up available, which is a short time period relative to the long disease time course that may span several decades. Reconstructing biomarker trajectories from these data sets requires new modelling techniques that can bring together cross-sectional and short-term longitudinal data at unknown time points to reconstruct a common progression pattern across subjects. Further challenges arise from misdiagnosis (either cases not having the disease in question, or controls having pre-symptomatic disease), mixed pathology, and sparsity of data points at the beginning and end of the disease time course.

Traditional statistical analysis techniques estimate biomarker trajectories by assuming a priori knowledge of where each data point lies along the disease time course. Hence, the majority of studies of neurodegenerative disease biomarker progression[8,9] rely on the use of a priori clinical classification as a patient staging measure and then compare biomarkers across groups. This reliance on clinical staging limits the temporal resolution of the biomarker progression to only a few stages, e.g. in Alzheimer's disease: 'cognitively normal', 'mild cognitive impairment' and 'Alzheimer's disease'. Recently a new family of truly data-driven statistical models[10-12] have emerged that do not require prior knowledge of the stage of each individual along the disease time course. This is a major advantage, as it allows for a complete picture of disease progression incorporating the full set of biomarkers, and with much higher temporal resolution. In this review we focus on these models, giving an overview of the different types that have been applied to neurodegenerative diseases so far; and the future potential of such data-driven disease progression models.

The event-based model[10] describes

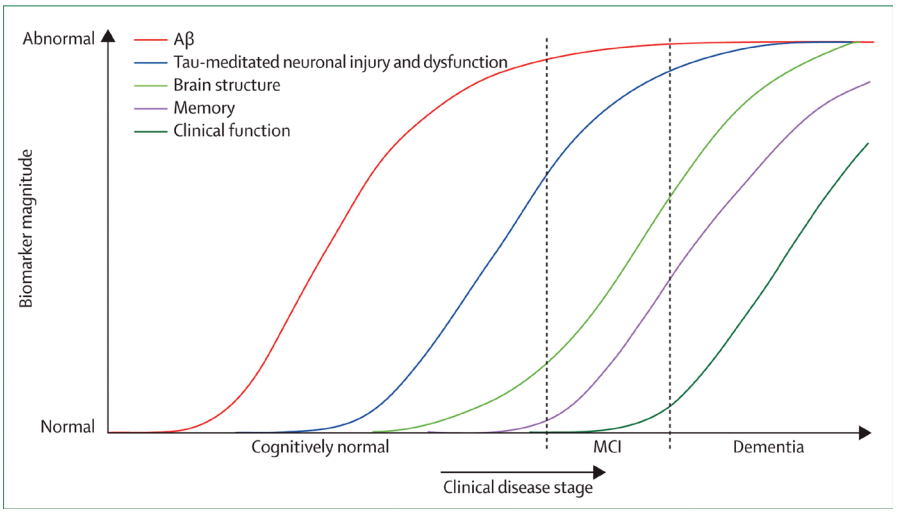

Figure 1: Dynamic biomarkers of the Alzheimer's pathological cascade. Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment. Reprinted from reference 1.

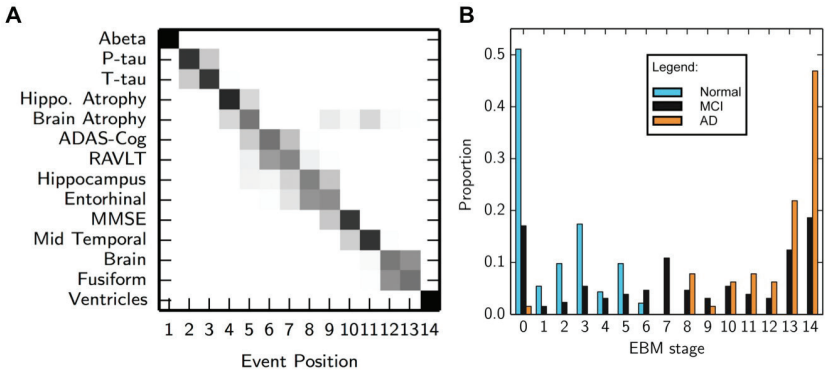

Figure 2: (A) Positional variance diagram showing the distribution of event sequences in apolipoprotein E (*APOE*) ε4 allele carriers. The diagram shows the uncertainty in the maximum likelihood event ordering estimated by taking MCMC (Markov chain Monte Carlo) samples using the Event Based Model (EBM). Each entry in the positional variance diagram represents the proportion of MCMC samples, in which events appear at a particular position in the sequence (x-axis). This proportion ranges from 0 in white to 1 in black. The y-axis orders events by the maximum likelihood sequence. Where rows have a single black block on the diagonal, the ordering is strong and permutations of those events are unlikely. Grey blocks show that permuting the order of the events has little effect on the likelihood so their ordering is weak. (B) Proportion of patients in each diagnostic category at each EBM stage. Each EBM stage on the x-axis corresponds to the occurrence of a new biomarker transition event. Stage 0 corresponds to no events having occurred and stage 14 is when all events have occurred. Events are ordered by the maximum likelihood event sequence for the whole population. Abeta = amyloid-β; P-tau = phosphorylated tau; T-tau = total tau; RAVLT = Rey Auditory Verbal Learning Test; MCI = mild cognitive impairment; AD = Alzheimer's disease. Reprinted from reference 13.

disease progression as a series of events, where each event corresponds to a particular biomarker becoming abnormal. The unique property of the event-based model is that it directly encodes, and thus estimates from the data, the ordering in which biomarkers become abnormal, or, more strictly, observably different from normal levels. This sequence of events provides a simple and intuitive description of disease progression, as well as a natural patient staging system – at stage X, the first X events have occurred. The event-based model has been applied to recover the sequence of regional neurodegeneration in both familial Alzheimer's disease and Huntington's disease.[10] More recently it has been modified for the more challenging application to sporadic neurodegenerative diseases[13] (Figure 2), and applied to determine the sequence of abnormality in sporadic Alzheimer's disease for a multi-modal set of biomarkers, including CSF measures of amyloid-beta and tau, regional volumetric and rates of atrophy measures from MRI, and cognitive test scores. Young et al[13] further demonstrate the clinical utility of the event-based model as a patient staging system, providing state-of-the-art classification accuracy for separating cognitively normal and Alzheimer's disease subjects, and for predicting conversion from cognitively normal to mild cognitive impairment and mild cognitive impairment to Alzheimer's disease. Another key strength of the event-based model is its probabilistic formulation, which provides measures of confidence in both the sequence of biomarker abnormality events across the population, and an individual's model stage. The event-based model naturally extends to differential diagnosis by providing a likelihood of each candidate neurodegenerative disease, which is achieved by fitting an individual's set of biomarker measurements to each corresponding biomarker sequence. One limitation of the event-based model is that it doesn't incorporate any information on the time between events or the rate of biomarker decline, which somewhat limits its utility for prognosis and monitoring.

Differential equation models[11,14-17] can be used to reconstruct an average cohort-level biomarker trajectory, which is continuous in contrast to the discrete description of the event-based model. The models use short-term follow up biomarker measurements to provide samples of the gradient of a single common biomarker trajectory and integrate a differential equation to determine a best-fit or 'average' trajectory for the cohort. For example, Jack et al[17] determine the time taken for amyloid accumulation to go from a normal to an abnormal level by fitting a differential equation model to data from serial amyloid-PET scans, finding that it takes approximately 15 years to go from a normal standard uptake value ratio (SUVR) of 1.5 to an abnormal SUVR of 2.5. Villemagne et al[11] (Figure 3) perform a similar analysis to determine the time taken for several biomarkers to go from normal to abnormal, including amyloid-PET, hippocampal atrophy, episodic memory, gray matter volume and non-memory cognitive domains. Differential equation models have potential as a disease staging, monitoring and prognostic tool as they provide the rate of biomarker decline over the disease time course. Stochastic differential equation models[18] can further express deviations from this average, providing prognostic information at the individual level. However, they model each biomarker individually, and so there is no guarantee of correspondence across disease stage and prognosis estimates between different biomarkers.

Self-modelling regression approaches[12,19] bring together data from multiple biomarkers to estimate biomarker trajectories over a common disease timescale. Short-term follow up data from each individual provides samples of a common set of biomarker curves, which are used to estimate the population-level shape and rate of biomarker decline, as well as each individual's position and rate of decline. As with differential equation models, the biomarker curves represent the average biomarker dynamics for a population. Donohue et al[12] (Figure 4) use self-modelling regression to determine the trajectories of cognitive test scores, regional brain volumes from MRI, PET imaging measures, and CSF levels of amyloid-beta and tau. Jedynak et al[19] formulate a similar model that uses cognitive test scores, CSF amyloid-beta and tau, and hippocampal volume on MRI to estimate a 'disease progression score', which is a continuous measure of disease stage that can be used as a time proxy. Self-modelling regression approaches provide continuous disease staging, monitoring and prognostic measures that incorporate information from multiple biomarkers. A key advantage of these models is that they provide a very complete picture of the disease, which can aid detailed disease

understanding. Potential disadvantages are that they have many more parameters to estimate than simpler models like the event-based model, so may be less stable; and the complex picture has a less straightforward interpretation than the discrete description, which may limit clinical utility.

To date, these data-driven models have shown compelling results that provide valuable insights into neurodegenerative disease progression patterns, particularly in Alzheimer's disease. However, they remain an emerging area of research, and all the current models share a number of limitations and assumptions that are important to consider when interpreting results. One strong assumption that all the aforementioned models make is that all subjects follow a common progression pattern. Although some models allow for subjects to deviate from this common progression pattern, these deviations are assumed to be small, and none allow for subgroups of subjects that follow completely different progression patterns. Such outliers are likely given the inherent heterogeneity of sporadic disease data sets, which contain some proportion of subjects with alternative neurodegenerative diseases, as well as mixed pathologies and a wide range of subject demographics. For this reason, practical applications of data-driven models often focus on more homogeneous population subgroups,[11-13,17] for example subjects with increased genetic risk of developing the neurodegenerative disease of interest. Another assumption is the independence of biomarkers: although the models express temporal correlation of biomarker trajectories over the disease time course, they assume independence at any given time point. In practice, biomarkers often co-vary, for example amyloid-PET and CSF measures of amyloid-beta are measures of the same underlying pathology and are therefore strongly correlated. Failure to model this covariance tends to cause underestimation of the variance of progression patterns across the population. Data-driven models further assume that data is available from the full disease time course when in reality the data points may be sparse at the beginning and end of the disease progression, which may influence the estimation of biomarker trajectories.

Future developments in disease progression modelling offer numerous exciting opportunities. Adaptations to characterise the heterogeneity in sporadic disease data sets are certainly possible, for example by using mixture models or distributions of event-sequences or biomarker trajectories, which is desirable for the application of these models on an individual level in clinic. This will help separate measurement noise from inter- and intra-subject variation depending on genetic, lifestyle and demographic information. The high temporal resolution of data-driven models is promising for their use in patient staging and disease monitoring. The discrete stages of models like the event-based model

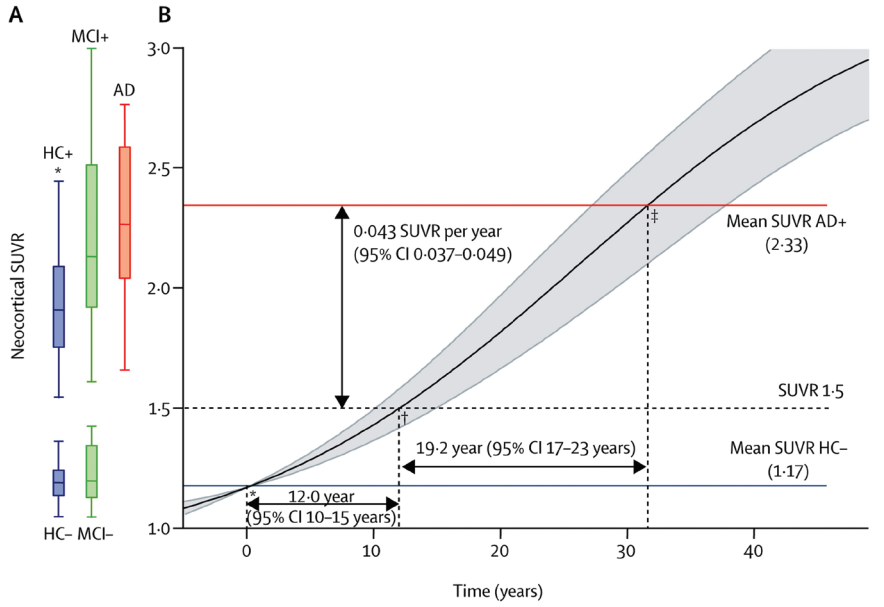

Figure 3: The natural history of Aβ deposition in sporadic Alzheimer's disease. AD=Alzheimer's disease. MCI=mild cognitive impairment. ^{11}C-PiB=Carbon-11-labelled Pittsburgh compound B. SUVR=standardised uptake value ratio. Aβ=amyloid β. (A) While there were no significant differences in SUVR between participants with MCI and AD with high Aβ burden (2·31 [SD 0·43] for MCI+ and 2·33 [0·36] for AD+), the mean values for healthy controls with high ^{11}C-PiB retention (HC+) were significantly lower (1·98 [SD 0·24], *p=0·0002). (B) Aβ deposition follows sigmoidal kinetics over time, where it takes 12 years to go from a mean SUVR of 1·17 (SD 0·09) noted in healthy controls with low ^{11}C-PiB retention (HC–) to reach the 1·5 PiB SUVR threshold. It then takes another 19 years to go from the 1·5 SUVR to the mean SUVR of 2·33 (0·36) observed in established AD. As disease progresses, the rates of Aβ deposition start to slow, trending towards a plateau. The shaded area represents 95% CIs. The horizontal dashed line represents the SUVR threshold (>1·5 or <1·5) discriminating between high or low ^{11}C-PiB retention. *Aβ accumulation begins. †Aβ positivity threshold is crossed. ‡Mean SUVR of established AD. Reprinted from reference 11.

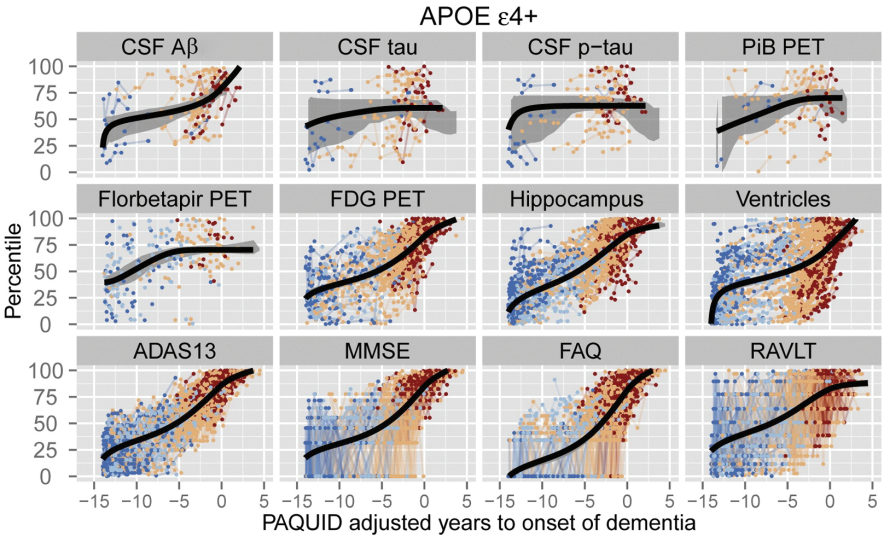

Figure 4: Alzheimer's Disease Neuroimaging Initiative (ADNI) apolipoprotein E (*APOE*) ε4 allele carriers. Each of the mean trajectories is superimposed over the subject-level observations from 570 *APOE* ε4 individuals, coloured by diagnosis. Colours represent diagnosis at ADNI baseline – cognitively normal (CN) in dark blue, early mild cognitive impairment (EMCI) in light blue, late mild cognitive impairment (LMCI) in light red, and Alzheimer's disease (AD) in dark red. Shaded grey regions, where visible in the top panels, represent bootstrap 95% confidence bands. Time has been adjusted using long-term "Personnes Agées Quid" (PAQUID) Mini-Mental State Examination trajectories so that time zero represents the estimated time to onset of dementia. Aβ, amyloid-β; p-tau, phosphorylated tau; PiB, Pittsburgh compound B; FDG, fluorodeoxyglucose; ADAS13, the 13-item Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; FAQ, Alzheimer's Disease Cooperative Study Functional Activities Questionnaire; RAVLT, Rey Auditory Visual Learning Test. Reprinted from reference 12.

align well with general medical practice, but continuous models provide more useful prognostic information. Future models designed for clinical use might combine elements of both, allowing continuous prognostic estimates, but also subdividing the progression into discrete stages. Data-driven models also present exciting opportunities for differential diagnosis; the ideas are somewhat robust to common problems such as missing data and differing study designs, so the models provide a natural framework for making information about different neurodegenerative diseases compatible. Such work will also enhance

basic disease understanding by highlighting the most discriminative features for differential diagnosis. New types of model yet to be explored include spatiotemporal models (e.g. network models[20]), which so far have relied on a priori clinical staging, but new approaches are emerging that may help avoid this limitation.[21,22]

Data-driven models are an emerging area of technology with major potential benefits to neurodegenerative disease research and clinical practice, and with wide potential further application to any disease or developmental process. They can provide quantitative multi-modal pictures of the full disease time course for improved understanding of disease mechanisms to inform drug discovery; they naturally combine different types of information for earlier and more accurate differential diagnosis, and subject-specific prognostic information; they provide fine-grained staging scores or systems for more precise patient stratification supporting clinical trials for developing treatments and ultimately treatment deployment. Research is ongoing to refine this emerging technology into a practical tool in medical development and practice.

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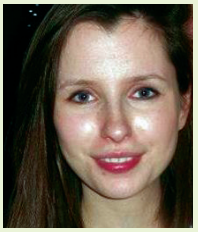
Oral therapies in relapsing remitting multiple sclerosis – Part 3



Lilia Dimitrov
is studying graduate medicine at Barts and the London School of Medicine and Dentistry. During her undergraduate degree in Neuroscience and Experimental Psychology at the University of Oxford, she specialised in neurodegenerative disease and since then has continued to pursue her interest in Neurology.

Ben Turner
is Consultant Neurologist and Honorary Senior Lecturer at Barts Health NHS Trust and UCLP. Dr Turner is a General Neurologist with a Sub-Speciality interest in Multiple Sclerosis. Currently Dr Turner is Chief UK Investigator for several phase III clinical trials, and therefore has extensive knowledge of the range of disease modifying therapies available to MS patients.

Correspondence to:
Dr Turner,
Department of Neurology,
Barts Health, The Royal London,
Whitechapel E1 1BB,
E: benjamin.turner@bartshealth.nhs.uk

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Di-methyl fumarate (Tecfidera™)

Introduction

In the first and second part of this three-part series of articles, we looked at the sphingosine-1-phosphate receptor modulator fingolimod and the pyrimidine synthesis inhibitor teriflunomide respectively. Dimethyl fumarate (DMF, Tecfidera®), the most recent oral therapy to be approved, will be the subject of this final article.

In January 2014 the European Medicine Agency (EMA) licenced DMF for the treatment of adult patients with relapsing and remitting multiple sclerosis (RRMS) and in August 2014 NICE recommended DMF as a possible treatment for people with active RRMS that isn't highly active or rapidly evolving severe RRMS. The starting dose of Tecfidera is 120 mg twice a day, after seven days, the dose is increased to the recommended dose of 240mg twice a day.

Mechanism of Action

The active ingredient of Tecfidera is the oral formulation of dimethyl fumarate $C_6H_8O_4$ (DMF / BG-12). DMF was developed following the successful use of Fumaderm® (Biogen-Idec, Weston, MA, USA) for psoriasis in Germany.[2] Psoriasis like MS is believed to have an autoimmune pathogenesis. The use of fumaric esters in autoimmune conditions is based on the evidence that these compounds activate Nrf2 transcriptional pathway with subsequent upregulation of elements involved in the antioxidant response.[3] These effects ultimately result in the inhibition of pro-inflammatory mechanisms and may promote a neuroprotective effect.[4]

DMF is rapidly cleaved into the active metabolite monomethyl fumarate (MMF) by esterases in the alkaline environment of the intestine. Ingestion with food delays maximal levels from two to five hours, with longer delays seen, the higher the fat content, but the total drug absorbed remains equivalent.[5] MMF is metabolised to fumaric acid and citric acid before being broken down to CO_2 via the Krebs cycle, as well as glucose, cysteine and acetylcysteine conjugates. Elimination occurs over eight hours with exhalation of CO_2 being the primary route accounting for approximately 60% of the Tecfidera dose.[6] Renal and faecal elimination are secondary routes of elimination. DMF and MMF seem to have little potential for drug interactions with no significant P450 (CYP450) inhibition or induction and low protein binding.[5]

Efficacy

DMF has been studied in psoriasis, rheumatoid arthritis, Crohn's disease, in addition to MS in greater than 18 studies, and for longer than four years in a subset of patients enrolled from the two pivotal RRMS Phase III trials (DEFINE and CONFIRM) into the long-term safety extension study ENDORSE.[7-9]

DEFINE and CONFIRM followed the Phase II study which revealed significant anti-inflammatory activity in RRMS.[10] Both Phase III studies were randomised, double-blind, placebo controlled, multi-centre international trials and enrolled over 1200 patients each. They both contained two active arms using DMF at 240mg twice a day (BID) and 240mg three times a day (TID) compared to a placebo arm randomised on a 1:1:1 ratio. CONFIRM contained an additional open label comparator arm of GA, however the study was not powered to demonstrate superiority of DMF to glatiramer acetate (GA) but just compare GA to placebo. Only the results from the DMF BID (treatment dose) will be reviewed here (Table 1).

The primary outcome of DEFINE was the proportion of patients who had relapsed at the end of the study at two years.[7] The result was a relative risk reduction in relapse of 49% for the DMF arm compared to placebo ($p<0.0001$). Secondary endpoints were the more familiar annualised relapse rate (ARR) and rate of confirmed disability progression. Both were reduced in the DMF arm; ARR by 53% (0.172 versus 0.364 respectively, $p<0.001$) and the rate of confirmed disability progression by 38% ($p=0.005$). A subset of 540 (44%) of patients formed the MRI study, the outcomes are also summarised in Table 1.

The second phase III study pretty much did what it said on the tin. CONFIRM found ARR (the primary endpoint) was significantly reduced by 44% for DMF compared to placebo (0.224 versus 0.401 resepctively, $p<0.001$).[8] Although not directly comparable to DEFINE a secondary endpoint of CONFIRM was proportion of patients who relapsed at two years which showed a 34% relative risk reduction compared to placebo ($p=0.002$). Disappointingly the confirmed disability progression endpoint was not significant. As in other studies that have failed to show a significant effect on accumulation of disability it has been suggested the failure of significance is due to lack of change in the placebo arm however this can only be supposition. CONFIRM contained a sub group of 681 patients who participated in the MRI sub-study, the results are again shown in Table 1. The open label comparator arm of GA was useful as an anchor demonstrating the expected 29% reduction in ARR compared to placebo (0.286 versus 0.401, $p=0.0128$), suggesting the DMF results are what would be seen in the real world.

Safety

In both DEFINE and CONFIRM there were no significant differences in serious adverse events and

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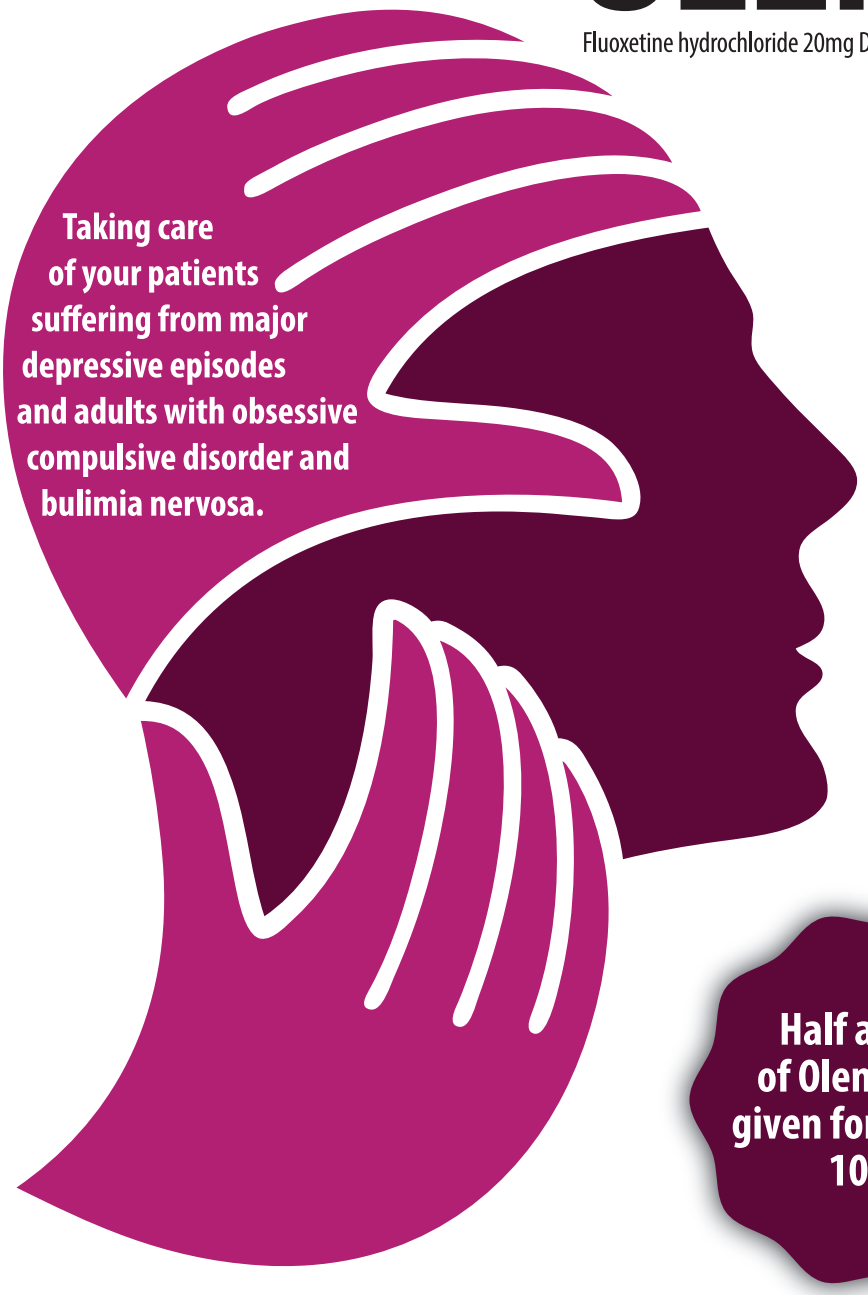

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PRESCRIBING INFORMATION: Olena 20mg Dispersible Tablets Fluoxetine hydrochloride. **Presentation:** Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20mg fluoxetine. **Indications:** *Adults:* Major depressive episodes, obsessive-compulsive disorder and bulimia nervosa. *Children and adolescents aged 8 years and above:* Moderate to severe major depressive episode. **Dosage and administration:** For oral administration. *Adults and Elderly:* The recommended dose is 20mg daily which may be increased gradually to a maximum of 60mg. Caution is recommended when increasing the dose in elderly. *Children:* The starting dose is 10mg/day given as half of a tablet. Abrupt discontinuation should be avoided and the dose should be gradually reduced. **Contraindications:** Hypersensitivity to any of the components. Combination of fluoxetine with MAOIs. **Precautions and warnings:** Caution should be exercised when used in children and adolescents under 18 years of age, seizures, mania. Lower dose is recommended in patients with hepatic dysfunction. Patients with cardiovascular effects, fructose intolerance and patients taking St. John's wort should be cautious. An adjustment of dose is recommended in patients experiencing weight loss, diabetes, suicide/suicidal thoughts, haemorrhage and mydriasis. **Interactions:** Serotonergic drugs, phenytoin, lithium, tryptophan, CYP2D6 isoenzymes, oral anticoagulants, alcohol and other SSRIs. **Pregnancy and lactation:** Fluoxetine can be used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour. Increased risk of cardiovascular defects when used in first trimester. It is known to be excreted in human breast milk. **Undesirable effects:** *Common:* Headache, nausea, insomnia, fatigue, diarrhoea, anxiety, nervousness, restlessness, tension, libido decreased, sleep disorder, abnormal dreams, disturbance in attention, dizziness, lethargy, somnolence, tremor, vomiting, dyspepsia, dry mouth, palpitation, QT prolongation, cardiac arrhythmias, flushing and blurred vision, oesophageal pain, hypotension and increased risk of bone fractures in patients receiving SSRIs and TCAs. (Please refer Summary of Product Characteristics for detailed information). **Overdose:** Symptoms of overdose include nausea, vomiting, seizures, cardiovascular dysfunction and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. **Legal category:** POM. **Basic NHS cost:** £3.44 for 28 x 20mg.

Marketing authorisation Number: PL 12762/0475. **Marketing Authorisation Holder:** Amdipharm Mercury Company Limited (AMCo), 1st Floor, Capital House, 85 King William Street, London, EC4N 7BL. **Date of preparation:** October 2013. **Date of revision:** December 2013.

Ref 1: NHS electronic Drug Tariff, NHS business service authority. Part VIIIA products F.[online]. [Accessed on 03/12/13]. Available at http://ppa.org.uk/edt/December2013/mindex.htm

Adverse events should be reported to the local regulatory authority. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Amdipharm Mercury Medical Information via telephone on 08700 70 30 33 or via e-mail at medicalinformation@amcolimited.com.

UK/OLE/AD/105B/2014 Date of preparation: June 2014

Table 1: Summary of DMF efficacy across Phase III clinical trials

Clinical outcome	DEFINE (n = 1234 , 24 months)		CONFIRM (n = 1417, 24 months)		
	DMF BID	Placebo	DMF BID	GA	Placebo
Proportion of relapses at 24 months (%) – p value	27 < 0.001	46 –	29 < 0.001	32 < 0.05	41 –
Annualised relapse rate at 2 years – p value	0.172 (p ‹ 0.001)	0.364 –	0.224 < 0.01	0.29 < 0.01	0.401 –
Disability progression confirmed at 3 months during 24 month study period (%) – p value	16 = 0.005	27 –	13 not sig	16 not sig	17 –
Mean no. Gd+ lesions – p value	0.1 < 0.001	1.8 –	0.5 < 0.001	0.7 < 0.001	2.0 –
Mean no. of new or newly enlarging T2 lesions – p value	2.6 < 0.001	17 NA	5.1 < 0.001	8.0 < 0.001	17.4 –
Mean no. of T1 hypo-intense lesions – p value	NA –	NA –	3.0 < 0.001	4.1 < 0.001	7.0 –

all adverse events between the active and placebo arms, including the GA group.[7-8] The events that occurred more frequently in the DMF groups were flushing with around 40% versus 6% in placebo, and any gastrointestinal events 50% versus 40% in placebo.[7-8] The number of patients that discontinued treatment due to flushing was around 3% and for gastrointestinal events 4% across studies.[7-8] Importantly these side effects were most marked in the first month and then declined. They can also be reduced by taking DMF with food, or taking acetylsalicylic acid prior to taking DMF has been shown to be beneficial over a short period.[11] In the current Summary of Product Characteristics (SmPc) for Tecfidera it is also possible to reduce the dose to 120mg DMF BID for up to four weeks, to allow the side effects to settle.[12]

In both studies lymphocyte counts were reduced by 30% on average with 6% of patients having levels <0.5x109/L.[7-8] Importantly there was no increase in serious infections in this group. Indeed there was no significant difference in the incidence of infections across the study arms. Interestingly dermatologists do use lymphocyte counts as a marker of treatment effect with Fumaderm.[13]

Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥3 times the upper limit of normal (ULN) were seen, respectively, in 5% and 2% of patients treated with placebo and in 6% and 2% of patients treated with DMF. These were all transient or reversed on drug withdrawal and none led to hyperbilirubinaemia or hepatic toxicity. Discontinuation due to raised transaminases was similar between DMF and placebo at <1%.

Proteinuria occurred in approximately 9% of those taking DMF but this was not dissimilar to the placebo group, and there was no significant difference in all renal events. The MS study has not revealed nephropathy or renal impairment and psoriasis studies have only noted clinically insignificant haematuria and leucocyturia that was present similarly between treatment and placebo groups.[2]

In the pivotal studies discussed here there was no indication of increased malignancy. ENDORSE has reported 14 cases of malignancies of differing types and locations in 13 patients.[9]

There is no evidence from animal studies to suggest DMF is associated with reduced fertility.[14] Animal studies have shown reproductive toxicity, so DMF is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception.[12] Obviously with the pregnancy registry a picture of risk will develop.

Finally looking at CONFIRM the number of patients who withdrew from treatment was similar across placebo (36%), DMF BID (30%), and GA (25%). For DEFINE the figures were placebo (35%) and DMF BID (31%). In DEFINE there was a death in each of the DMF arms, both from accidents. One death occurred in CONFIRM in the TID arm from a MS relapse.

On going to press there has been a fatal case of progressive multifocal leukoencephalopathy (PML) in a patient treated with DMF for four and a half years, they had been on placebo for 2 years in a pivotal trial and entered the open label phase. It appears the crucial feature was the patient was lymphopenic throughout the treatment phase, therefore immunocompromised and predisposed to PML.

Box with Monitoring recommendation for DMF

Before treatment

- Recent complete blood count (i.e. within 6 months) should be available.
- Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) and hepatic function (e.g. ALT and AST) are recommended prior to treatment initiation.

During treatment

- Full blood count after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated
- Renal and hepatic function blood tests at 3 and 6 months, and then every 6-12 months.

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Rapid reliable 'on' for Parkinson's disease

APO-go PEN provides rapid and reliable 'on' **for patients with morning akinesia**, reducing time to on by an average of 40 minutes[1]

APO-go® Apomorphine hydrochloride
PRESCRIBING INFORMATION Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly. and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers**: APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision**: March 2014 For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information on 0870 851 0207 or dso@genuspharma.com

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1. AM IMPAKT Study interim results. Presented at International Parkinson and Movement Disorder Society. Treatment of Parkinson's Disease: Past, Present and Future. March 2014, Miami, Florida, USA.

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Vocational Rehabilitation following Traumatic Brain Injury:
What is the evidence for clinical practice?

Dr Julie Phillips, PhD, MA, Dip COT,
qualified as an Occupational Therapist in 1980. Since 1998, she has worked at the Nottingham Traumatic Brain Injury Service (NTBIS) where she completed a PhD at University of Nottingham in 2013 entitled: 'Return to work after Traumatic brain injury: A cohort comparison study and feasibility economic analysis.' She is currently working as both an OT with the NTBIS and a research OT on the Facilitating Return to work through Early Specialist Health based interventions trail (FRESH aka Return to work after traumatic brain injury) at the University of Nottingham.

Dr Kate Radford, PhD, MSc, DipCOT
is an Occupational Therapist interested in vocational rehabilitation (VR) and participation. Current research includes an HTA funded feasibility trial of early TBI VR, evaluation of an early intervention to support work return after stroke and a trial of peer coaching to promote leisure after stroke.

Correspondence to:
Dr Julie Phillips,
Research Occupational Therapist,
Division of Rehabilitation Research,
B114 Medical School,
Queens Medical Centre,
Nottingham NG7 2UH, UK.
Email: julie.phillips@nottingham.ac.uk

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Summary

- For those in work prior to their TBI, only around 41% are in work one and two years later.
- Evidence suggests that vocational rehabilitation may increase return to work rates but the evidence is not robust. Better quality research is needed.
- More detailed reporting of vocational interventions are needed to inform clinicians and services.

Introduction
Traumatic brain injury (TBI) typically affects young adults with potentially many years of working life ahead of them. For people who were in work prior to their injury, return to work (RTW) is a common goal. However, a systematic review of RTW rates for people with TBI who were in work prior to their injury found that approximately 41% were in work at one and two years post TBI.[1] Since TBI is a leading cause of morbidity worldwide in young adults,[2] this discrepancy between what people with TBI want and what they achieve is important. The question is does the research evidence inform clinicians how to help a person with TBI return to work?

What is Vocational Rehabilitation?
Vocational rehabilitation (VR) is described as 'whatever helps someone with a health problem stay at, return to or remain in work'[3] This broad description is intended to encompass efforts to support work return or job retention from all sectors. However, it is unhelpful in terms of encouraging researchers and clinicians to describe and explain TBI VR.

A variety of VR models for people with TBI exist both within and between countries but the terminology used to describe them is inconsistent. For example; in a systematic review of VR approaches following TBI, Fadyl et al[4] identified three broad models, which they called 'programme based', 'supported employed' and 'case co-ordination'. Hart et al[5] conducted a similar review also concluding there were three models, which they called 'train and place', 'place and train' and 'a combined model'. Tyerman et al[6] identified four models: 'brain injury rehabilitation programmes with added VR elements', 'VR models adapted for TBI', 'case coordination/resource facilitation models', and 'consumer-directed models'. Unfortunately, few of these models have been adequately described or rigorously evaluated.

Some studies report on job retention,[7] others on finding new work,[6] while most report on the clinical and work outcomes of service users evaluated as part of a rehabilitation service or system.[8] Detailed descriptions of the interventions delivered are rare.[9] Studies must describe not only the specific details of the intervention but also the context and structure essential to its delivery so clinicians can be informed about which interventions work for whom and in what context. Without this information emerging evidence of effective interventions cannot be replicated by clinicians and outcomes cannot be compared at an individual or service level.[10]

Does Vocational Rehabilitation increase return to work rates for people with TBI?
Systematic reviews of the effectiveness of VR to help people with TBI RTW have produced mixed evidence. For example:- Ownsworth et al[11] reviewed 50 studies of prognostic indicators of RTW after TBI and found moderate evidence that providing VR was predictive of post TBI employment. Kendall et al[12] reviewed 26 studies of TBI rehabilitation and employment outcomes and found that people with TBI who received VR were more likely to return to work and returned sooner than those who did not. However, other reviews of TBI and VR have found inconsistent evidence.[13,14] In a recent systematic review of 80 studies of TBI and VR, Saltychev et al[15] said the results were inconclusive due to methodological problems of the studies reviewed. In summary, the evidence suggests vocational rehabilitation may increase return to work rates for people with TBI but it is neither robust nor overwhelming.

It appears both knowledge of VR and specialist knowledge of TBI are required to increase return to work rates in this population. A retrospective study of the outcomes of 107 people attending a pan-disability specialist VR centre, found people with TBI did less well in returning to work due to the cognitive and behavioural problems people with TBI experience.[16] Both Powell et al[17] and Ponsford et al[18] examined the effectiveness of TBI specialist community rehabilitation on work outcomes independently. Both concluded that vocational rehabilitation is needed in addition to TBI rehabilitation if work outcomes are to be improved for people with TBI. Thus, the evidence suggests that specialist knowledge of both VR and TBI is more likely to improve the chances of someone with TBI returning to work.

Predicting work return
Many studies of TBI examine predictive factors for RTW. Factors predictive of a poor work outcome include having no job pre-injury, age over 40 years, longer duration of hospital stay and reduced functional ability on discharge.[11,13,14]

Interestingly, these studies did not find initial Glasgow coma scores were predictive. However, a clinician cannot alter these predicative factors once a patient is at home. Additionally, the evidence for any predictor is not sufficient to decide who should benefit from VR.

Other factors may be more important determinants of whether a person with TBI returns to work. In a national prevalence study examining predictors of work return in 855 stroke survivors, Lindstrom et al[19] found psychological factors such as believing work to be important and having the support of significant others were more important determinants of success than the stroke specific deficits. These personal factors such as the person's and families attitudes, beliefs and understanding of the impact of the TBI on the individual and environmental factors such as increasing an employer's understanding of TBI, suggesting appropriate work modifications are factors that may be influenced by a clinician as part of a VR programme. Clinicians and people with TBI want to know 'what is the best way to return to and remain in work?' However, this level of detail is currently lacking in research studies. For example, does educating the employer increase a person with TBI chances of successfully returning and maintaining work and is this more effective done at the work site or is a letter or phone call enough? Does spending time helping both the person and family understand the impact of the TBI help increase RTW success? To date, the research evidence does not appear to be answering these practical questions faced by clinicians but is what is needed to inform service design and delivery.

Methodological limitations

Evidence for the effectiveness of VR and TBI is difficult to assess because of methodological problems with studies themselves.[1,4,15,20,21] The problems included differing definitions of 'work', a variety of outcome measures, heterogeneous study populations, different time scales, small-scale studies, limited descriptions of the interventions and poor quality research methodology. Sixty-eight of the 80 studies reviewed by Saltchev et al were observational, small, retrospective, single centre pre-post intervention designs. The lack of randomised controlled trials (RCTs) and cohort comparison studies make it difficult to determine whether any increase in employment rates is due to natural recovery, the intervention received or other factors such as publication bias. Nevertheless, the preponderance of small studies suggests that the centres involved feel their interventions warrant attention, yet at the same time highlights the problem of insufficient numbers of TBI people in each centre to conduct adequately powered trials.

There is clearly a need for rehabilitation researchers and clinicians to use an agreed minimal dataset of outcomes that enable meaningful comparison of outcomes[6,22] see Box 1. There is also a need for funding and infrastructure to support multicentre randomised trials, more epidemiological evidence on the expected rate of recovery and long-term outcome after TBI including the longer-term financial and social impact of rehabilitation or lack of access to it.[23]

Box 1: Suggested minimum data set for use by clinicians and researchers when describing TBI VR

- Agreed definition of work e.g. paid/unpaid work, full/part time education, voluntary work, house keeper.
- Work metrics e.g. full/part time, number of hours worked, type of job and status, salary, type of enterprise i.e. private business, self-employed, statutory.
- Who the intervention was aimed at:-
  - type of injury i.e. traumatic, acquired, stroke,
  - injury severity e.g. minor, moderate, severe,
  - time post injury.
- Details of people receiving the intervention (sex, age, pre-injury work status, medical details such as length of hospital stay, other injuries).
- Aim of the intervention e.g. job retention, work readiness, new work?
- The setting i.e. in-patient, outpatient clinic, community, work?
- Who delivered the intervention e.g. Occupational therapist, case manager (plus a description of their expertise and any specific training).
- Details of the intervention the patient received i.e. individual, group, work site visit, goal setting, cognitive rehabilitation, fatigue management (see reference 10).
- Involvement of others e.g. family, employers, other health and social care providers, other agencies e.g. Department for Work and Pensions, independent, charitable sector?
- Agreed set of standardised outcome measures to include work ability, functional ability, mood, quality of life, work readiness, and carer strain.
- Workplace accommodations implemented, including graded return to work, changes in job roles/responsibilities/hours, supernumerary and other support e.g. extra breaks, specialist equipment.
- Frequency and length of intervention and agreed length of follow-up i.e. 1, 2 5 and 10 years.
- Economic data to include costs of intervention (number of times patient seen x cost per hour of each therapist seen), number of GP and consultant appointments, change in persons wages (same, more or less than prior to injury), welfare benefits claimed, effect on carers income, cost to employers.
- Compliance rates and any problems.

What is missing?

Very few studies examine the cost-effectiveness of VR following TBI which is surprising given the known importance of cost effectiveness in health based decision making.[24] There are no RCTS or trials of TBI VR, which include economic evaluation.[25] However, the few studies that have addressed cost issues look promising. Although not a formal cost benefit analysis, Murphy et al[8] compared the cost of providing VR and offset it against savings in state benefit payments in those who successfully return to work and stated that costs were recuperated within 26 months. A UK cohort comparison study found that a specialist TBI team intervention with VR from an occupational therapist (OT) cost approximately £75 more per participant over one year from a health and social care perspective compared to usual care.[26] This equated to one extra community OT visit. Those with access to the specialist TBI team reported a better quality of life and more had returned to work than those in usual care at one year. Given the young age of the TBI population, the success of any VR may last for many years and affect not only the person but also family members. These additional benefits need to be captured in studies attempting to measure resource use.

If health service commissioners are to be convinced of the value of providing TBI VR, studies that demonstrate the economic burden that TBI poses to families, the health service and society needs to reflect the cost savings that effective intervention may provide. This is problematic given that the impact of successful intervention such as job retention, reduction in anxiety and depression and improvements in quality of life tend to occur in the longer term. Additionally, reductions in resource use from successful VR such as fewer GP appointments, reductions in mental health service use, and reduced dependency on welfare benefits occur in different departments from the NHS department originally providing the specialist intervention.

Finally, clinicians have no control over the fluctuating nature of the economy or competitive job markets, therefore factors that they can influence need to be measured, even when return to work is not possible or advisable. For example, knowledge of TBI and adjustment to its effects for the both the individual and family, work readiness, employer awareness, workplace accommodations are some of the possible factors that may warrant being measured that can be influenced by clinicians.

Conclusion

People with TBI want to return to work, clinicians want to deliver evidence based interventions and commissioners want to commission cost effective rehabilitation services. Unfortunately, the existing evidence for VR following TBI is too limited to draw accurate conclusions about its effectiveness or cost effectiveness. A consensus on a minimum data set and well-designed high quality studies are essential to provide the evidence needed to support practice, inform commissioning and ensure people with TBI are given the best chance of returning to work following a TBI.

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People in need of our services need staff who offer clinical expert knowledge, skills and passion backed up by experience and research Good clinical leadership of our services is self evidently important in ensuring the patient experience is as good as it can be.

There are currently in the UK National Health Service a number of leadership training schemes. In the East of England scheme which is entering a third year of operation, a recent Quality Improvement programme has brought together a wide range of clinicians and administrators to be "Quality Improvement Fellows".[i] Fellows had the chance to benefit from mentors and training provided by staff at the King's Fund. I heartily recommend colleagues to look for similar opportunities.[ii]

In one of the sessions of this training programme participants enjoyed a moment to reflect on the art of story-telling. Graphic designer Graham Ogilvie was present, drawing simple cartoons of the messages conveyed by participants who had been asked to turn their quality improvement projects into a story. Participants were encouraged to use the form of a story, to think about characterisation, heroes and villains, start and ending, and other ingredients. I considered that Gemma has done this in such a compassionate and warm way, clearly demonstrating the point of Dementia Friendly wards.

There is a broader point: as scientist-practitioners we need to ask ourselves how we should best translate findings from projects (service improvement, audits or research) into documents that motivate action. Have we shared our learning in a way that ensures widest possible benefit?

Sometimes translation of research can be done in ways that are very familiar to us all, and it is perhaps not a fairy story to imagine that Services can improve through leadership such as is provided by people like Gemma. Gemma's story provides an illustration of this because we are readily drawn into narratives. I wonder if you find yourself thinking about what you could do differently as a result of reading this?

Perhaps a different style of article to those usually published in this journal, I was really interested to note how it has been possible to allude to a rich literature in a short space. But most of all, I found this story to make for a compelling read and I hope our regular readers do too.

Andrew Bateman, Rehab Editor (and Quality Improvement Fellow in the same cohort).

i. https://www.eoedeanery.nhs.uk/page.php?page_id=2781
ii. http://www.kingsfund.org.uk/leadership

Gemma Holland

is a specialist Occupational Therapist working on The Dual Frailty Unit at Watford General Hospital, West Hertfordshire Hospital Trust. She has completed a Quality Improvement Fellowship run by Health Education East of England and the King's Fund. Her interests are in dementia and delirium. She is currently involved in the design and implementation of a Delirium Recovery Programme in collaboration with Dr Tammy Angel Consultant Geriatrician and finalist for HSJ Inspirational Woman of the year 2014.

Correspondence to: Email: Gemma.Holland@whht.nhs.uk

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Fighting the chains of stigma in dementia and delirium

John and Mary had been married for 52 years, they lived a happy and fulfilled life together, they had raised their family, John had worked hard as an engineer travelling around the country and now they were enjoying their retirement together. John was extremely active, he enjoyed spending time with his family, working in his shed completing DIY tasks and maintaining his vegetable filled beautiful garden.[8,11] Over a period of time a dark fog began to envelop John. He would be part way fixing the tyre on his bike and he would forget what he needed to do next.[7,8] He began to get muddled with what day it was and forget the word that he wanted to say in conversation with his grandchildren.[7] John began to withdraw in himself, he felt invisible, he felt his family would talk about him as though he was no longer there, he lost his appetite, he refused to drink, he would wear the same clothes for days and would stare out onto his beautiful garden lost in his own world.[4,7,8] The fog deepened, John began a downward spiral, falling deeper and deeper into the unknown.[4,8,15] Eventually John found himself trapped in a dungeon, guarded by dragons and tied up in chains of stigma, his voice and identity lost.[4,15] Scared and confused by his surroundings John looked for ways to escape but the dragons kept pulling him back.[5] John tried to fight them, he kicked and hit, but the dragons overpowered him with potions that made him tired and sleepy.[3]

One day John woke from his sleep to find a beautifully weaved basket full of items that made up his identity – a photo of his and Mary's wedding day, the boiler suit he loved to wear when outside working and his gardening book that he loved to flick through whilst having a cup of tea in the morning.[2,8,10,11,15] As John picked each item from the basket a calmness descended upon him and before his eyes an angel appeared – a Dr Angel – who granted him three wishes.[6,10,11]

John's first wish was to get his voice back – he no longer wanted to be invisible and he wished his thoughts and beliefs could be heard.[3,8,11,13] His second was to be able to do the activities he previously loved to do, to have a role, and feel useful and needed.[7,8] His third wish was to have the opportunity to go home to his lovely wife and familiar surroundings.

'illustration by graham@ogilviedesign.co.uk

Suddenly the fog began to lift and the dungeon was no longer a dungeon, it had transformed into a dementia friendly ward.[4] The environment was a large space with clearly visible signs to direct to the toilet. John was encouraged to walk around. He had access to a garden and fresh air.[4,5,7,13,15] The dragons became health professionals that would call John by his name, listen to his wishes and act upon his request for support of his care needs.[4,7,12] They communicated with John with an improved level of respect and were mindful that John may find complex sentences difficult to process.[7,13,14] They were patient and understanding when John struggled to clearly express himself, but gave him the opportunity to have his say.[2,7,12] John was enabled to complete his own personal care tasks and given support when needed.[8,13] They encouraged him to dress in his own clothes and worked with John at a level he was able to understand. John became involved in ward activities. His skills in DIY were actively encouraged to help build the raised flower beds in the garden and care for the many herbs and flowers donated to the ward.[3,5-7,10-13] Alongside the increase in his activity, John's appetite began to return and when he woke one morning craving a bacon and egg sandwich, one was sought after.[1,8] Mealtimes were encouraged to be social events where all sat at a brightly coloured table set for the gentlemen in the bay.[5,11] Drinks were offered throughout the day and snacks of sandwiches, cakes or fruit were freely available to pick at when peckish.[6,7]

John and Mary were included in the discussions of his ongoing medical care and his voice was loud and clearly heard when planning his discharge from the ward.[3,6] John was given the opportunity to go home, with 24 hour enabling support that reduced over a 21 day pathway. John and Mary were involved in the process of tailoring the care to enable and support John's needs, re-establish his routine and set himself goals.[3,7,9,13] Mary was given support in managing the times when John became frustrated with his slow recovery and difficulty in understanding what had happened (that it had seemed like he was living in a nightmare).[3,14,15] For the 21 days the carer, Mary and John could seek advice and support over the phone, and home visits took place to refresh John's goals and to see his functional improvement in his home environment.[7,8] The carer encouraged John to engage in the activities he previously enjoyed.[2] Things began to settle and one day into the second week Mary looked out of the kitchen window and began to smile at the sight of John and the carer caterpillar hunting around the vegetable garden, sneakily eating the blackberries until their tummies ached.[2,8,10,13] The pathway provided education to Mary on the ways to reduce the risk of the dungeon and dragons returning again. By monitoring John's medication compliance, nutritional and fluid intake, bowel and bladder habits as well as being aware of changes in John's behaviour.[3,4,7,14,15] Midway through the pathway a mental and physical health review in ambulatory care signed John off from the acute hospital and he was referred on for diagnosis, advice and support on dementia.[14] John no longer felt invisible and alone. He began to realise that this was going to be a new stage in his and Mary's journey together.[2,7,8] For John the fog was still there, but it was lighter now and the sunshine began to break through.[4,8]

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Cell therapy for Huntington's disease

Anne E Rosser
is a Clinical Scientist specialising in stem cell neurobiology, striatal development and cell therapy. As Professor of Clinical Neuroscience in Cardiff University she co-directs the Brain Repair group with SBD, and as Consultant Neurologist at the University Hospital of Wales she runs the specialist Huntington's disease research clinics in South Wales, including clinical trials of drug, rehabilitation and cell transplantation.

Stephen B Dunnett
is a Behavioural Neuroscientist specialising in animal models of basal ganglia disease and preclinical development of methods of cell transplantation and rehabilitation. He is a Professor in the School of Bioscience, Cardiff University, and co-directs the Brain Repair group with AER.

Correspondence to:
Prof Anne E Rosser,
Brain Repair Group,
School of Biosciences,
Cardiff University,
Museum Avenue,
Cardiff CF10 3AX, UK.

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AER and SBD co-direct the European FP7 repair-HD consortium, working to deliver a first-in-man stem cell-based cell transplantation trial in HD.

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Summary

- Early clinical trials of foetal striatal cell transplants in HD patients have shown initial indications of functional response, but the recovery has not (as yet) been shown to be reliable or sustained.
- In experimental animals, foetal striatal transplants can integrate into host circuitry and alleviate aspects of motor and cognitive disease, maintaining the prospect for an effective reconstructive cell therapy in HD patients.
- Cell transplantation can also be used for sustained and controlled delivery of neuroprotective and trophic molecules into precise deep brain targets, opening the prospect for alternative strategies to cell therapy which should be seen as complementary, not mutually exclusive.

What is meant by "cell therapy"?
Cells can be used therapeutically for two purposes: either to deliver substances to the brain, for example molecules that can support the survival of host neurons, or to replace cells that have been damaged or lost to the disease process with the aim of repairing the damaged neural circuitry (see Figure 1 for a schematic illustration of the principles of circuit repair versus substance delivery). The two purposes place different demands on the donor cells, and will be dealt with separately in this article. However, we emphasise that the different mechanisms of promoting recovery of function need not be mutually exclusive and may, at least theoretically, be combined into one more effective treatment strategy.

Why consider HD for cell therapy?
Huntington's disease (HD) is of interest as a target for cell therapy for two reasons:first because it is a devastating and currently untreatable disease with biological features that render it suitable for a cell therapy approach, and secondly because it is a good model of neurodegeneration more generally and may therefore allow the establishment of principles that can be generalised to other degenerative conditions.

Searching for treatments of HD
HD is said to affect around 6 per 100,000 in Europe, North America and Australia, although this may be a significant under-estimate of its prevalence.[1] Despite significant advances in the understanding of the pathophysiology and clinical phenotype of HD since discovery of the gene in 1993,[2] there is currently no available disease-modifying treatment for HD and symptomatic treatments are very limited and largely anecdotal rather than evidence-based.[3] While the molecular and cellular processes underlying HD are clarified and targeted, pharmacological treatments are sought and trialled, it is logical to pursue all rational strategies, which currently include empirical screening of existing drug libraries; therapies that potentially target the pathophysiology such as histone deacetylase inhibitors; RNA inhibition and similar strategies that developed from the understanding that HD is largely due to a toxic gain of function of the mutant protein; and replacement of cells based on the understanding that medium spiny neuron (MSN) damage plays an important role in the evolution of symptoms.[4]

Why is HD a suitable target for cell replacement?
HD presents biological features that makes it a good cell therapy target. In particular, the cell loss in HD, at least in the early to moderate stages of manifest disease, is predominantly of the medium spiny neurons (MSNs) of the striatum,[5] which normally constitute approximately 85% of the neurons in the intact human striatum. Thus, there is a focal area of degeneration and a single cell type to provide a target for cell placement. Although it is theoretically possible that cell therapy will eventually be suitable for diseases with diffuse degeneration extending over widespread and or involving multiple cell types, at this stage of evolution of the technology cell transplantation has been more successful when based on targeting replacement of a single or restricted range of cell types with a focal location amenable to direct surgical targeting. Of course, both the specificity of the cells injected and the "focal" nature of the disease are both relative rather than absolute constraints, and each is considered further below.

Another reason for investigating HD as a clinical target for cell replacement is that it presents a valuable model of neurodegeneration more generally in which to work out how to achieve success in cell therapy. There are compelling reasons for considering regenerative medicine in a wide range of neurodegenerative conditions. Together, these conditions represent a very large disease burden and, for the vast majority, there is no disease-modifying treatment currently available. Targeted pharmacological treatments are likely to be a long way off for most of these conditions, in which the detailed pathogenesis is not fully elucidated, and yet many of them are amenable to cell replacement because their anatomy and distribution of neuronal cell loss is understood.

There are several reasons why HD is a good model in which to understand the principle of

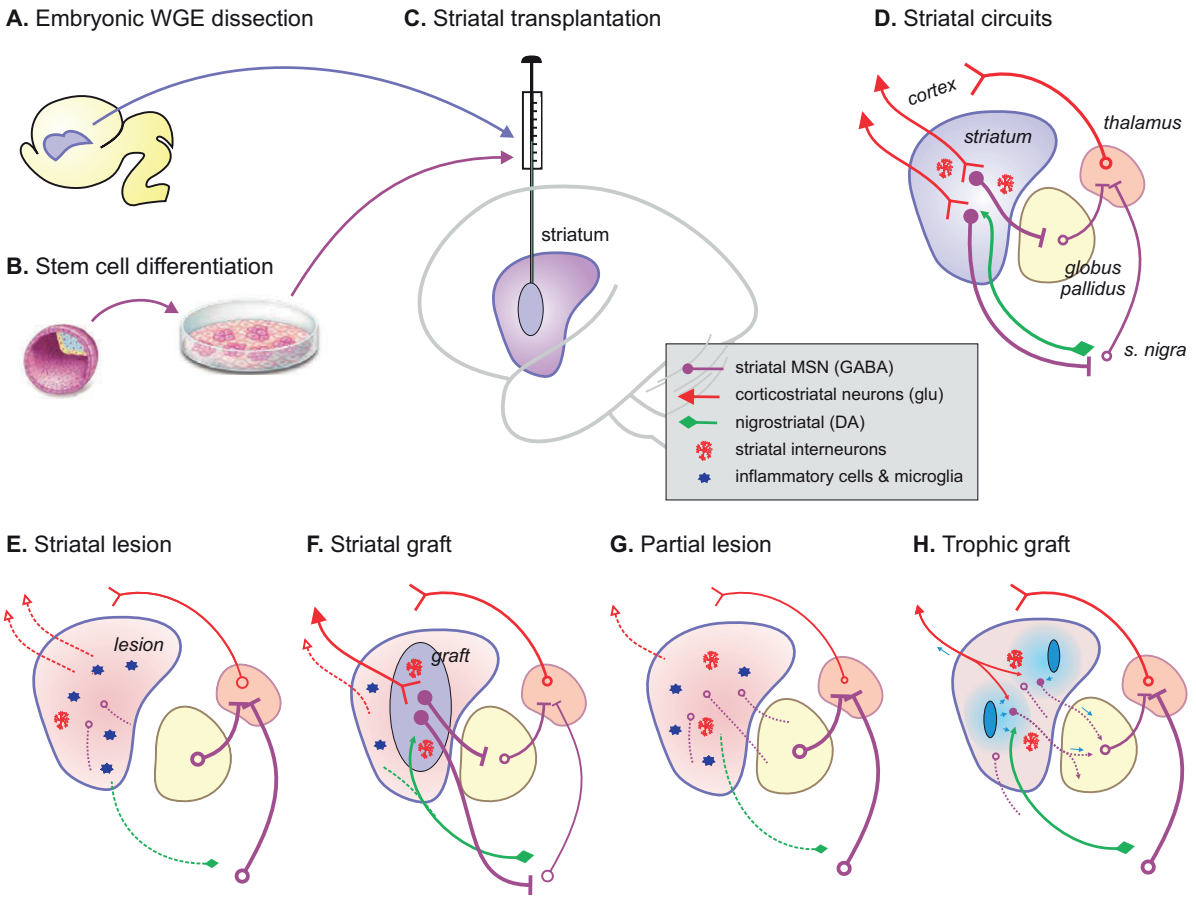

Figure 1: Schematic illustration of transplantation of primary embryonic ganglionic eminence (A) or stem cell-derived striatal neurons (B) into the host striatum (C), illustrating potential mechanisms of action:normal striatal connections relay information from cortex via intrinsic striatal processes to pallidum, thalamus and midbrain (D). Excitotoxic lesions destroy the striatal medium spiny projection neurons, accompanied by inflammatory and glial responses, yet with relative sparing of interneurons and host afferent terminals (E,G). Secretory grafts may provide a source for diffuse or locally regulated release of neuroprotective, anti-inflammatory and trophic factors, which enhance host neuronal survival, axon growth and plasticity, but do not replace essential circuit neurons destroyed by the lesion (H). By contrast, some grafts (such as fetal WGE) can replace lost striatal neurons leading to reconstruction of host neuronal circuits and recovery of function through true circuit repair (F). It remains undetermined by which mechanism the modest functional effects reported following stem cell-derived neuronal transplants are achieved.

cell repair. First, it is an autosomal dominant condition with full penetrance and a simple genetic test is available, which means that it can be diagnosed with certainty in life and indeed, prior to symptom manifestation.[6] This substantially increases the power of clinical trials aimed at disease modification, specifically, seeking to alter the course and progression in HD. Secondly, following the two decades after the discovery of the gene there has been substantial advancement of understanding of the underlying pathophysiology[7] and the clinical phenotype[8], underpinning a significant amount of work to optimise clinical outcome measures (for example reference 9), and building a platform for clinical trials.[8] Thirdly, there are multiple animal models (rodent, primate and model organisms), which provide an excellent laboratory platform for discovery and preclinical work-up of novel therapeutics. All of this means that HD is well set up for studies of novel therapeutic strategies.

The donor cells:circuit repair versus secreted molecules

The major difference between donor cells for molecule delivery and those for circuit reconstruction is that the former need to be capable of sustained secretion of the target molecules, but do not necessarily need to differentiate into a specific neural phenotype (see Figure 1A-D, G, H), whereas the latter must be capable of differentiating precisely to the cell type that are lost in the disease process, and then integrating appropriately into the host circuitry following transplantation (see Figure 1A, C-F).

Some cells such as mesenchymal stem cells appear to naturally secrete trophic-like molecules, although they may also be genetically engineered to produce specific molecules such as BDNF,[10] but they do not necessarily need to differentiate into neural cells themselves. There is some evidence starting to emerge suggesting that molecule delivery may be appropriate for HD. For example, mesenchymal stem cells engineered to produce BDNF (which is reduced in the brain in HD) appear to improve symptoms in animal models of HD and a clinical trial is now ongoing.[11] Available evidence suggests that the functional effects in this case are not due to structural repair whereby the exogenous graft cells replace those lost in the disease, but rather to the grafts acting as a vector for delivery of trophic and tropic stimuli to promote regenerative plasticity and endogenous reorganisation within the damaged host circuits. In the interest of space, this will not be considered further here and the focus will be circuit repair. Although presenting more stringent requirements on the cells, this strategy has a greater potential to generate improvements in function through structural repair of the core pathology. Our goal is true "brain repair", i.e. reversing the disruption of host circuits by replacement of lost neurons and authentic reconstruction of the damaged brain networks, thereby allowing restitution of the neural processing required to underlie normal complex motor and cognitive function.

In order for donor cells to be able to replace those lost to the disease process, they need to differentiate very precisely into the appropriate phenotype; to the extent that cell replacement is specific, cells that have some, but not all, of the features of the target cell may not demonstrate effective repair and functional improvement.[12] A good example of this is replacement of nigrostriatal dopamine neurons in Parkinson's disease: the target cells are A9 group of dopamine cells in the midbrain, and transplant studies have shown

that the adjacent A10 dopamine neurons are considered less capable of generating full repair and functional recovery;[12] indeed, other dopaminergic neurons of hypothalamic or olfactory origin do not show comparable integration in the host brain and are without functional impact on even simple motor features associated with nigrostriatal degeneration. The same appears to be true for replacement of pure populations of MSNs in HD. Other non-striatal GABAergic neurons are relatively ineffective in striatal lesion animals, and indeed the better functional results are achieved when the full population of striatal neuronal types – interneurons as well as MSN projection neurons – are included into the grafts.

Furthermore, in order to integrate into the host neuropil, donor cells must be immature and not fully differentiated, but at the same time must be committed developmentally to a specific phenotype so that once transplanted they are able to continue their differentiation pathway in a cell-autonomous fashion. This balancing act is crucial; a cell that is too immature will not have received all the developmental signals it needs to instruct it to become a specific neural subtype, so it may arrest at an immature developmental stage or follow a 'default' differentiation pathway. A cell that has completed differentiation and undergone significant maturation may not survive the transplantation process and quickly loses the early potential for rapid growth, neurite extension, connecting to appropriate targets and integration into the host neuronal network. In practical terms this means that there is a "developmental window" during which cells can be successfully transplanted for circuit reconstruction, corresponding roughly to the peak in embryonic birth dating of the target neuronal population. For human embryonic striatal cells for use in HD, this translates to approximately week 8-10 foetal tissue.

Evidence that circuit repair can work

Transplantation of developing primary foetal MSNs (i.e. MSNs obtained directly from the fetal striatum without manipulation in culture, as distinct from stem cell-derived neurons differentiated to MSN fate) into the degenerating striatum has been shown to ameliorate motor and cognitive deficits in animal studies, primarily in rats and primates. Such studies have allowed the mechanisms underlying the functional improvement to be explored, and have shown that implanted cells can integrate into the circuitry and make functional synaptic connections, providing that they were of the appropriate phenotype (i.e. destined to become MSNs) and were procured within the appropriate developmental window.[13] Evidence of functional efficacy in humans comes from a seminal French study that reported human fetal-derived graft survival and significant improvements in both motor and cognitive function in three patients.[14] Enhanced FDG-positron emission tomography signal in the frontal cortex of these individuals suggested that the implanted cells had integrated into the striatal neural circuitry and made functional connections with relevant cortical regions.[15] The improved cognitive function is particularly interesting, as there have been few treatments for cognitive impairment across any neurodegenerative disease. Clearly, further evidence is required with greater patient numbers; indeed, the French HD network has recently completed a larger transplantation study, which will hopefully be reported within the coming year. Overall, it is reasonable at this stage to conclude that there is proof-of-concept evidence that transplantation of developing MSNs into the striatum can produce functional improvements in at least some patients with HD. The task now is to improve reliability and to identify which cells, patients, and conditions provide the optimal functional response.

Challenges and the way forward

A major challenge for the field is that primary foetal cells are scarce and cannot be easily standardised, so a renewable, quality-assured source of cells is required. Various stem cell sources can be readily expanded in number, easily cryopreserved and are much more amenable to processing according to good manufacturing practice (GMP) principles. There are several human stem cell sources being actively explored for potential cell replacement therapy in the central nervous system, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), foetal neural precursors (FNPs), adult neural stem cells, and somatic stem cells derived from blood, bone marrow or other peripheral lineages.[16] The most critical factor in producing neurons with the capacity to repair the damaged adult brain is that they must reliably and accurately replicate the phenotype of those cells lost to the disease process. A small number of groups have demonstrated that neurons with MSN characteristics can be differentiated from human stem cell populations with survival of MSN-like cells post-transplantation.[17-20] Successful generation of MSN-like neurons has been achieved by exposing ESC-derived neuronal precursors to developmental signals thought to be important in MSN differentiation and a number of published protocols report differentiation of MSN-like cells in vitro and following transplantation into a rodent model of HD, where they provided variable functional improvement with some evidence that the cells could integrate into the host neural circuitry to receive dopaminergic input from the midbrain and glutamatergic input from the cortex while projecting fibres to the globus pallidus.[17-20] Several of these studies have also reported modest functional effects,[18,19] although it remains as yet undetermined the extent to which MSN-like stem-cell derived neurons have the same capacity to reconstruct the damaged host neural circuitry to a comparable degree to that readily achieved by authentic developing MSNs (see Figure 1). It is important to note that these cells are not currently ready for clinical translation, although that remains a topic of active investigation[21] and progress to date indicates that the current barriers to translation are surmountable.

A second challenge will be the fact that, although the focus of degeneration in HD is the striatum, there is also degeneration of extrastriatal regions. In the French studies outlined above, function continued to improve over the first few years, but patients started to decline again by six years post-surgery, most likely due to continued degeneration of the striatum.[22] While the improvement was not permanent, there are a number of reasons why transplantation should still be considered as a therapeutic option. First, this scale of improvement is substantially greater than any other attempted treatment of HD to date. Second, whereas the initial focus and mechanism of the spread of HD pathology within the diseased brain remains unresolved, it remains plausible that replacement of lost neurons in a critical node such as the striatum may provide additional support to afferent neurons and reduce prion-like transmission of toxic products,[23] thereby slowing the cell-to-cell spread of pathology within the neural circuitry. Third, cell replacement therapy is still at an early experimental stage and, judging by history such as renal transplantation in the 1960s where rather limited early success ultimately led to great medical advances, it is highly likely that optimising technical aspects and parameters (such as transplantation earlier in the disease) will produce more sustained effects. Finally, it would seem logical to ultimately consider cell replacement therapy in combination with disease modifying drugs once they also become available.

Transplantation as a therapeutic approach in Huntington's disease is at an early but exciting stage. Experimental models suggest that a surgical replacement strategy is feasible; multiple cell sources are available; multiple potential mechanisms of integration and functional recovery remain plausible. In the opinion of these authors, all options should remain open for theoretical and experimental exploration, without prejudice or pre-supposition, and dogmatic declarations of the 'correct' approach remain premature.

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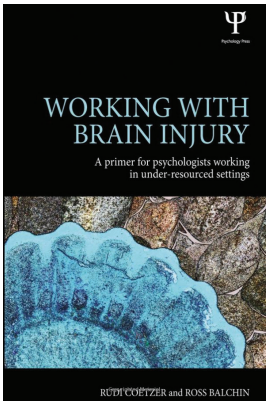
Working With Brain Injury

A Primer for Psychologists Working in Under-resourced Settings



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Christian E Salas Riquelme, PhD, Head Forward Centre, Manchester.

"Clinical neuropsychology is a curious beast, representing equal measures of science and art. It encompasses the science of brain-behaviour relations and the art of understanding, as well as the applications of these skills on many different levels. Neuropsychology can be very technical on the one hand, but can also demand extraordinary compassion and humanity on the other (p. xiv)". This definition, offered by the authors of this book, is the simplest, but most insightful, definition I ever heard of the experience of working as a clinical neuropsychologist. To become acquainted with, and comfortable around, this curious beast may take years, or decades, particularly if you lack the necessary guidance. And if you search for advice in books, most of the clinical neuropsychology books [the so called handbooks] work like a taxonomy listing followed by a cookery book. They describe the syndromes in detail, tell you how to differentiate one from another, and then they suggest a set of recipes. These books may give you important knowledge in understanding the beast's behaviour, as a map of South America will give you important information regarding the locations of cities and where one country limits to another. However, such abstract books tell you nothing about the experience of becoming a traveller – how to behave in a specific culture, which places to visit, where to ask for help. These books say nothing about the journey of becoming a clinical neuropsychologist, the basic equipment you need to carry with you, or the basic skills that you need in order to do the job competently. This book by Coetzer and Balchin is a companion on the journey, a sort of travel guide on the continent of clinical neuropsychology.

There are several reasons why I am enthused about this book. Firstly, its writing style is very engaging. It touches every topic of relevance for our daily work, but does so in a clean and clear manner. There are no obscure technicalities; there are no overwhelming reference lists. This generates an impression of the voice of a mentor, a friendly narrator that is constantly engaging you in a conversation about the neuropsychological journey, with judicious warnings of peril. This encompasses practical tips [e.g. buy a brain model of your own, avoid making predictions] and reflective suggestions [e.g. choose your ideal neuropsychological battery and explain the reasons for this selection]. It is this intimate tone that makes the book uniquely useful for anyone [students of psychology or medicine, trainees, newly qualified psychologists] coming to work with brain injury.

The structure of this book is entirely consistent with its main goal: 'to create a self-study resource for the reflective practice of practical skills, as well as to function as a teaching resource' (p. xvi). It is organised into three main sections [each with several chapters] – basic foundations, clinical practice and professional issues. The Basic Foundations section offers a synthetic panoramic of several areas of knowledge that are relevant when working with brain damage, such as neuroanatomy, neuropathology, psychopathology, psychopharmacology, neuropsychological theory and special investigations. This is probably the least innovative section of the book, since it refers to topics commonly covered in handbooks. Nevertheless, the emphasis placed by the authors on the journey of becoming a clinical neuropsychologist provides some new insight. The section on Clinical Practice is extremely interesting, since it takes the reader, step by step, through the different actions he/she will perform on a daily basis: clinical assessment, neuropsychological testing, formulation, neuropsychological rehabilitation, psychotherapy approaches and record keeping. It is in this section where the practical tips, and the points of reflective practice, come into their own. The final section on Professional Issues is quite interesting too, since it moves the reader's attention away from the tasks involved in everyday work, to issues of professional development, such as professional practice, supervision, research/academia and management.

The reason underpinning this book's unique quality is that it is written by clinical neuropsychologists who have experienced first-hand what it is like to work with brain injury in under-resourced settings [South Africa and rural Wales]. This is a common reality across many countries [developing and developed], where the resources may not permit the delivery of full packages of rehabilitation in the conventional sense, or permit mentoring of junior colleagues at every stage. Coetzer and Balchin confront the limitations and seem aware that, in those contexts, less may be more. They know that learning a basic set of skills, which can be put then systematically into practice, can make a huge difference. Their book is a materialisation of this idea. I highly recommend this book to anyone interested in using clinical neuropsychology to help individuals with acquired brain injury.

Novel pathogenic antibodies give insight into the role of $GABA_A$ receptors in the central nervous system

Article being reviewed: Ohkawa T, Satake S, Yokoi N, Miyazaki Y, Ohshita T, Sobue G, Takashima H, Watanabe O, Fukata Y, Fukata M. Identification and characterization of GABAA receptor autoantibodies in autoimmune encephalitis. J Neurosci. 2014;34:8151-63.

David A Menassa
read bioenergetics at the University of Cambridge. In 2009, he was awarded a Clarendon PhD studentship to the University of Oxford to investigate the neuroimmune, neuroanatomical and neurophysiological mechanisms underlying autism and epilepsy. He is jointly supervised by Professor Angela Vincent, Dr Steven Chance and Dr Sven Braeutigam.

Katarzyna D Bera
read Molecular Medicine at Erlangen in Germany. In 2006, she was awarded a Wellcome Trust PhD studentship to the University of Oxford to investigate the pathogenicity of NMDAR antibodies under the supervision of Professor Angela Vincent. She subsequently read graduate entry medicine at Oxford and now works as an Academic Foundation Doctor in Bristol.

Correspondence to:
Katarzyna D Bera,
Academic foundation doctor FY1,
Southmead hospital,
Severn Deanery,
Bristol BS10 5NB, UK.
Email: katarzyna.bera@doctors.org.uk

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Summary

- Antibodies against the β3 subunit of GABAA receptors identified in patients with thymomas.
- Spectrum of autoimmune encephalitides extended with discovery of pathogenic antibodies to inhibitory channel.
- Identification of antibodies involved a comprehensive characterisation of pathogenicity.
- Clinically, improvement is observed but coincides with multiple interventions and does not directly address whether this may be due to a depression in autoantibody titres.
- Binding of antibodies may alter network excitability, as inhibitory neurotransmission is likely to be impaired.

Over the past decades, our understanding of the interactions between the immune system and the brain has been challenged. Research showed that antibodies against central nervous structures can be produced by our own immune system often without an identifiable cause. This can lead to loss of the target antigen and inflammation of brain tissue. These autoantibody-mediated conditions are collectively referred to by the term autoimmune encephalitides. Patients typically present with subacute onset of memory loss, psychiatric disturbance, confusion, seizures, and in some cases abnormal movements. The targets of these pathogenic autoantibodies have been identified as receptors or ion channel-associated proteins expressed in the central nervous system (CNS) – the N-methyl-D-aspartate (NMDA) receptors and the voltage-gated potassium channel (VGKC) complex proteins are the most commonly identified autoantibody targets. Whilst initially considered a purely paraneoplastic phenomenon associated with tumours outside of the CNS,[1] autoantibodies against CNS antigens were shown to be present in patients without an underlying, or diagnosed, neoplasm.[2]

Whether the autoantibodies are pathogenic per se, or whether they are merely a marker coinciding with a separate disease process are questions that have been the focus of study. Antibodies mediate their pathogenicity in several ways but the most common mechanisms are internalisation of their antigenic target, activation of the lytic complement cascade or directly interference with ion channel function (discussed in Vincent et al.[3] in more detail). Irrespective of their pathogenic mechanism, the first step always involves binding of the antibody to the antigen: an important paradigm, therefore, is that autoantibodies against cell surface receptors are more likely to be pathogenic than autoantibodies against intracellular antigenic targets.

To determine an autoantibody's pathogenicity, Koch's postulates on infectious diseases were modified to apply to autoimmune conditions.[4] Autoantibody-mediated pathogenicity can be assumed in cases where (1) an antibody-mediated immune response is present and (2) the antigen has been identified. Furthermore the postulates require that the disease be induced experimentally, both in a (3) passive transfer and (4) an active immunisation model.

Earlier this year, Petit-Pedrol et al[5] identified autoantibodies to the γ-Aminobutyric acid $(GABA)_A$ receptors in patients with encephalitis who presented with intractable seizures or status epilepticus with no tumours. The antibodies were shown to bind to the α1 or β3 subunits. Antibodies to the $GABA_A$ α1 and γ2 subunits have also been found in a proportion of patients referred for NMDA receptor antibody testing (Pettingill et al, submitted). $GABA_A$ receptors are postsynaptic GABA-gated pentameric channels made up from 2α, 2β and 1γ subunits surrounding a central ion-selective chloride channel. Their main function is to depress neuronal excitability.[6,7]

The paper by Ohkawa et al[8] identified novel autoantibodies to the β3 subunit of the GABA receptor in two patients who presented with clinical manifestations of confusion, personality changes, memory loss, and seizures and examined in more detail the possible pathogenic mechanisms. Both patients had invasive cancers of their thymus, which required surgical excision and radiotherapy. They were identified from a cohort of over 100 patients with suspected autoimmune pathology of the CNS by screening patient sera binding to primary hippocampal cultures. The

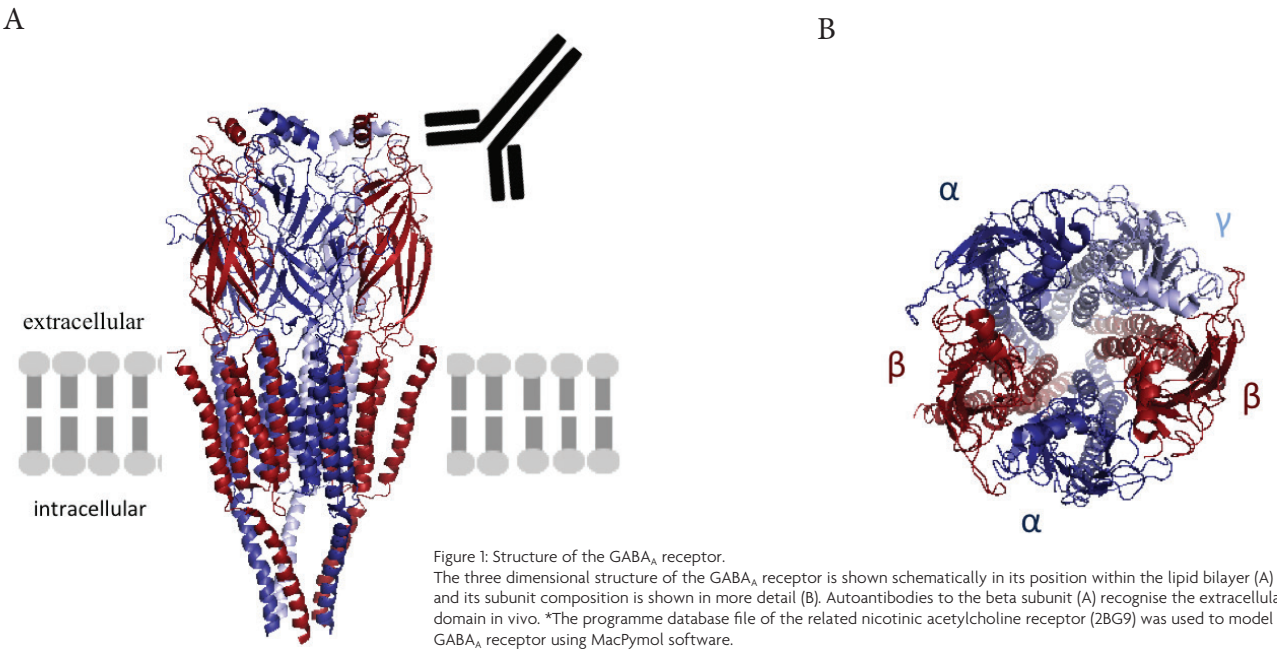

Figure 1: Structure of the $GABA_A$ receptor.
The three dimensional structure of the $GABA_A$ receptor is shown schematically in its position within the lipid bilayer (A) and its subunit composition is shown in more detail (B). Autoantibodies to the beta subunit (A) recognise the extracellular domain in vivo. *The programme database file of the related nicotinic acetylcholine receptor (2BG9) was used to model the $GABA_A$ receptor using MacPymol software.

identity of the antigenic target was examined by using a combination of immunoprecipitation and mass spectrometry. Expression of individual $GABA_A$ demonstrated that the autoantibodies bound an extracellular epitope on the β3 subunit. The autoantibodies did not bind other $GABA_A$ receptor subunits, though evidence of cell surface expression of individual subunits was not provided. However, a β3-subunit-specific knockdown experiment confirmed that the autoantibodies no longer bound the hippocampal neuron surface when the β3 subunit was removed from the channel complex. The autoantibodies downregulated surface $GABA_A$ receptors over 48 hours in neuronal cultures, consistent with the internalisation mechanisms; the reduction of cell surface ion channels was not mediated by the complement pathway. Additionally, the reduction in cell surface $GABA_A$ receptor levels was also matched by a depression in electrophysiological activity. These autoantibody-mediated effects were specific to patient serum obtained during the manifestation of CNS symptoms; archived serum from one of the patients predating the encephalitis did not affect $GABA_A$ receptor numbers or electrophysiological recordings.

Clinically, the distinction between paraneoplastic and non-paraneoplastic autoantibodies may aid the treatment decision: a sustained immune response raised against the neoplasm can be limited by excision of the tumour, whereas non-paraneoplastic autoantibodies can only be targeted by immunosuppressive therapy. Steroids, plasma exchange and intravenous immunoglobulins are often used as first step immunosuppressants, and more aggressive treatment approaches have been used for resistant or relapsing patients.[9] No large studies have been performed to date to compare treatment strategies.

Clinical improvement of one of the patients was seen after administration of immunosuppressive therapy (corticosteroids and intravenous immunoglobulins) combined with anti-epileptic drugs. The patient became seizure-free, though cognitive and psychological symptoms persisted. Autoantibody levels were quantified using a cell-based enzyme-linked immunosorbent assay (ELISA) prior to immunotherapy only and it remains unclear whether a depression in autoantibody titres following therapy may have coincided with the alleviation of symptoms. Patient two was treated with chemotherapy alone, and whether the improvement was due to a treatment-related immunosuppression or a reduction in tumour load affecting (paraneoplastic) autoantibody levels remains also unclear. As both patients had invasive thymomas, a paraneoplastic phenomenon may have been likely. Therefore, histological analysis showing the potential expression of $GABA_A$ receptor subunit within the tumour tissue would have been useful. The use of a semi-quantitative approach to measure autoantibody levels with cell-surface ELISA or similar methods, would have also allowed the investigation of the temporal relationship between clinical status and autoantibody levels more closely.

The presence of VGKC-complex autoantibodies in both patient sera further complicates the conclusion as to whether anti-β3 $GABA_A$ receptor autoantibodies are specifically responsible for the clinical features. It is also possible that the full spectrum of anti-VGKC-complex associated antibodies has not been identified as yet. Screening of larger patient cohorts with similar CNS features might be helpful in future to address whether $GABA_A$ receptor autoantibodies are solely linked to invasive thymomas and whether the co-existence of VGKC-complex autoantibodies is typical for this patient group. This detailed characterisation of the $GABA_A$ receptor autoantibody emphasises the importance for the continued screening for novel CNS antigens in patients with encephalitis-like symptoms.

Antibody-mediated pathology was once thought to be rare but since the discovery of autoantibodies against the NMDA receptors,[1] at least thirteen types of autoimmune encephalitis have been described in a rapidly expanding clinical field. Pathogenic antibodies against subunits of inhibitory receptors described to date have included those against the GlyαR1 subunit of the glycine (Gly) receptors,[10] and those against the B1 subunit of the $GABA_B$ receptors.[11]

Pathogenic antibody binding to synaptic cell surface or structural proteins of inhibitory channels is likely to interfere with inhibitory neurotransmission in the CNS. This would be supported by the cessation of seizures, a possible surrogate of hyperexcitability, when immunotherapy suppresses autoantibody titres. A close study of correlation of autoantibody levels in serum and cerebrospinal fluid and their temporal relationship to symptoms is thus important. Autoantibodies have been linked with hyperexcitability in the case of the VGKC-complexes,[12,13] $GABA_B$,[11] and Gly receptors.[10] 30-40% of neurons in the CNS use GABA as their neurotransmitter and inhibitory effects are predominantly mediated via the $GABA_A$ receptors. Okhawa et al[8] demonstrated that autoantibody levels depressed inhibitory currents of surface $GABA_A$ receptors but did not have any effects on excitatory currents mediated by AMPA receptors. It is likely that a prolonged exposure (>24 hrs) to

the antibodies may have altered excitatory neurotransmission as this could mimic better in vivo conditions. Local pathological inflammation may also contribute to excitability in vivo. A localised immune response with the subsequent release of cytokines and a possible element of complement activation might further impact onto local neuronal signalling pathways. Activated microglia and reactive astrocytes may alter the balance between excitation and inhibition in the milieu and may affect neuronal wiring through the formation of a glial scar.[14]

Blood-brain barrier integrity could be affected through cytokine-activated receptors on endothelial cells, leading to a further recruitment of immune cells to the CNS. Thus, the effects mediated by pathogenic antibodies against inhibitory channels calls for the need to develop comprehensive in vivo human studies and animal models to determine autoantibody-mediated pathogenicity on a molecular, network and more global level. Understanding how autoantibodies can cause specific symptoms would help us understand not only disease but also brain function.[2] Clinicians should be guided by the neuropsychiatric symptoms to identify whether an autoimmune cause should be ruled out mainly because the immunotherapy provides clinical improvements. The findings of Ohkawa et al[8] extend the clinical spectrum of autoimmune encephalitides to include the $GABA_A$ receptors and strongly suggest that future research should focus on further screening of larger patient cohorts to elucidate the downstream effects of autoantibody binding to postsynaptic receptors.

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Strategic Clinical Network for Mental Health, Dementia, Neurological Conditions, Learning Disability and Autism (MHDNL) Strategic Clinical Network (SCN) East of England *Epilepsy Event*

Conference details: 26 June, 2014; Stansted, UK. ***Report by:*** Juliet Ashton, Sapphire Nurse Consultant - Epilepsy Commissioning, Epilepsy Society and Victoria Doyle, Quality Improvement lead for Neurological Conditions, Coproduction and Dementia, East of England Strategic Clinical Network, NHS England.

Each of the twelve Strategic Clinical Networks (SCNs) have been tasked to improve services for people with neurological conditions. Services for people with epilepsy has been identified as a priority by all of the SCNs which is reinforced by the decision of the Royal College of GPs to highlight epilepsy as one of its clinical priorities for 2013 – 16.

The East of England SCN certainly lived up to its shared values of "Creating a shared purpose for transformational change" and "Putting patients, clinicians and carers at the heart of decision making" at the Epilepsy Event on June 26th. Over 100 delegates attended the event made up of service users, families, carers, Voluntary sector organisations (Epilepsy Action and Epilepsy Society), The National Development Team for Inclusion, Epilepsy Specialist nurses, Learning Disability nurses, Health Facilitator teams, Neurologists, Commissioners, Social care staff and GPs, to name but a few. The aim was to gather information from all the delegates across the network, sharing examples of good practice, coming together in workshops to identify what people with epilepsy want from their services and what matters most to them. This is the first event I have attended where there has been such a strong voice from the people with epilepsy: I believe the points raised will get listened to by the SCN and taken forward into positive actions.

The day commenced with an introduction and welcome from the morning chair, Dr Max Damian, SCN Clinical Lead, explaining one of the rationale for SCNs was 'To improve quality and outcomes through connecting services and efficiently using resources'. Dr Damian described the objectives for the day as: bringing together key interest groups involved in epilepsy care and highlighting their perspectives; to outline the elements of a pathway towards a better, more equitable service across the East of England and to identify how we can ensure strong collaboration between those involved in improving services.

This was followed by Dr David Bateman, National Clinical Director for Neurology, who discussed commissioning a better epilepsy service and highlighted the head line figures for the East,

- 16000 people with epilepsy in the East of England1000 people of which admitted with an unplanned admission(6.25%)
- £400,000 cost minimum?
- 17% are managed by neurologist
- Total bed days per year 3760

What is needed to address these figures are local services, an accurate initial diagnosis, good initial advice and support and appropriate long term care. Dr Bateman, demonstrated the new Public Health England Neurology Intelligence Network http://www.yhpho.org.uk/mhdnin, which provides indicators about risk factors, prevalence, access to services, outcomes and finance, and includes profiling tools in particular for epilepsy.

Dr Tejal Mitchell, Neurologist in Peterborough, gave an East of England and National perspective of the second National Audit

of "Seizure management in Hospital". She detailed the findings of poor policies for management of first seizures (62%), status epilepticus (68%) and onward care of seizure patients (56%).

Only half of people experiencing a first seizure were referred on to first seizure or epilepsy clinics. 54% of patients had access to Epilepsy Nurses and under 50% had seen an 'epilepsy specialist' in the previous 12 months. Dr Mitchell concluded that there is a need for a planned epilepsy pathway, to improve quality of care and clinical outcomes for patients, whilst increasing efficiency. She has also been working with the clinical commissioning group (CCG) on a business case for two band 7 ESN posts both of which have been appointed.

Vicki and Christian Raphael from Inclusion East and Matt Clark, Christian's personal assistant, talked about how to live a full life with epilepsy and a learning disability and what their expectations of the health team are, from the perspective both the patient and the carer. Christian is central in planning his own care and communicating what he likes and wants to do and his team support him completely. Their expectations are that if Christian is admitted to hospital, the health care professionals responsible for his medical care will communicate with other clinical teams so that everyone is aware of his needs. Christian, with support from his PA Matt, deliver training based on his personal experience of living with epilepsy, across the country. Vicki is a co director of Inclusion East, which is an organisation made up of families with similar experiences who provide a circle of support for each other. They also campaign for equality and social inclusion for people with learning disabilities and their families, with a focus on people who have complex needs. It was an inspirational and very well delivered presentation.

With a tough act to follow, Sarah Vibert and I, Epilepsy Society, discussed a new epilepsy commissioning tool being set up by a steering group involving, the Royal College of GPs, Epilepsy Society, Epilepsy Action, SUDEP Action, NICE, NHS England and pharma partners. We are pulling together a compendium of good practice across the UK as well as data on unplanned emergency admissions for people with epilepsy. This information is going to be discussed at a round table event with CCGs on November 20th.

Everyone assembled for the first workshop to address what the epilepsy pathway should look like, particularly at first seizure, diagnosis and long term management stages. Each group was balanced with a representative allocation of the delegates described above, the facilitators ensuring that everyone had an equal opportunity to voice their opinions, in particular the people with epilepsy. All the tables provided feedback on key points, with some great examples of good practice, in particular prompt access to a neurologist for an accurate diagnosis, an epilepsy specialist nurse to act as a sign post and the ability to see patients in a setting which suits the individual person with epilepsy.

Dr Alex Smallwood, GP and Bedfordshire CCG, chaired the afternoon session, introducing a fellow GP and RCGP Epilepsy Champion, Dr Greg Rogers, talking about the primary care element of services for epilepsy. Dr Rogers highlighted some statistics from a survey, Critical Times, conducted by Epilepsy Action in 2013, in which 34% of CCGs have a plan or intend to produce a plan for epilepsy and 17% of CCGs have appointed someone to lead on epilepsy. 34% of hospital trusts do not offer adults access to epilepsy specialist doctors and only 46% offer access to specialist nurses. Epilepsy Action have repeated the survey and are in the process of collating the results. It will be interesting to see if these statistics have changed and what has driven the change. He went onto illustrate how epilepsy is the fifth highest cause of emergency admissions amongst neurological long term conditions, arguing that now is the time to address epilepsy services across secondary and primary care. He went through the nine NICE epilepsy quality standards and asked how capacity could be increased to meet these standards? A suggestion is devolution of appropriate care to Practice nurses, GPs and Pharmacists with a special interest in epilepsy. For example perhaps GPs could review everyone who has required unscheduled care for epilepsy, within 2 weeks, to see if a remediable cause is identifiable?

Dr Mark Manford, Neurologist from Cambridge University Hospital, discussed shared decision making for new anti-epileptic drugs (AEDs) between primary and secondary care. He explained shared decision making should do exactly what it says, involving the neurologist, GP, person with epilepsy and their family if appropriate. He went on to say that the CCGs have a role in supporting GPs in deciding whether or not to accept clinical responsibility for prescribing and supporting trusts to resolve issues that may arise as a result of shared care.

I was very impressed with the quality of the speakers, their obvious interest and motivation to improve services and their commitment to keep people with epilepsy at the heart of decision making.

ECTRIMS Joint meeting with ACTRIMS, Boston 2014

Conference details: 10-13 September, 2014; Boston, USA. ***Report by:*** Alasdair Coles, University Lecturer in Neuroimmunology, Cambridge University.

"A bit thin this year," said my friend as she left. And I had to agree. No blockbuster news. No big trials. Rather a quiet ECTRIMS this year. The only record was the attendance: 9000 delegates from 70 countries. After due consideration, the committee-of-one has awarded this years' ACNR ECTRIMS prizes.

ACNR prize for the Most Motivating Presentation: the skipper of the yacht 'Sailing Sclerosis'

The yacht 'Sailing Sclerosis' sailed from Copenhagen in June to arrive in Boston a few days before the ECTRIMS meeting, crewed entirely by people with multiple sclerosis. The plan is to circumnavigate the world. The skipper, a Neurologist, described how he had been inspired by talking to a man with progressive multiple sclerosis; this blacksmith was depressed because he thought that he would never sail the world in the boat he had built. The Neurologist hit him across the back and told him to get sailing again. (Hopefully the Danish GMC did not hear that bit). The skipper's reflections on their journey so far were challenging, touching and humble. They promise to arrive in Barcelona in time for ECTRIMS next year. Well done to Biogen for sponsoring them.

ACNR prize for The Best Plenary Talk: David Hafler, Yale

David Hafler, one of the rock stars of multiple sclerosis biology, often gives the impression that the only work that is any good comes from his group. That is clearly not correct but annoyingly, it is not completely wrong. The new data he reported at this meeting was that

- Next generation sequencing of T cells from the periphery and brain of people with multiple sclerosis suggests that the common ancestral founders originates in the periphery, found in cervical lymph nodes (Stern Sci Trans Med 2014). So, Hafler says this proves that multiple sclerosis is triggered in the periphery first and does not arise because of a primary brain problem, like oligodendrocyte death. I am not sure you can be so sure. But the data is impressive.
- Eating at a fast food restaurant increases the proportion of CD4 T cells that are Th17.

Who would have thought! This observation led to the idea that increased salt concentration might drive pathogenic Th17 cells (Kleinewietfeld Nature 2013). Vijay Juchroo identified SGK1 as a salt-sensing kinase which is key to this effect (Nature 2013). New data shows that high salt both reduces the suppressive capacity of regulatory T cells and induces Th17, all induced by SGK.

- In nearly 40 years of research, no one has been able to differentiate the T cells of people with multiple sclerosis and normal healthy controls. Now, analysing memory CCR6+ T cells from patients with MS, using a novel T cell library technique, it seems that myelin-reactive T cells secrete more IFNg, IL17 and GMCSF, and less IL10, than controls.

ACNR prize for The Most Obvious Useful Research: Dr Jeffery and the FREEDOMS investigators

Our brains shrink as we get older. Those with multiple sclerosis have worse brain atrophy. An obvious questions is: does brain atrophy now predict worse disability in the future? This post hoc analysis of the FREEDOMS trial of fingolimod says Yes! The risk of worsening disability (so that you cannot walk unlimited distances, EDSS >4) at four years, is twice as likely if you have high rate of atrophy in the first two years. So, now you know.

The coveted ACNR Wooden Spoon Prize for the Worst Research: Dr Ratzer, from Copenhagen

This study has all the hallmarks of poor research. Firstly, the researcher attempts to answer a question that has already been flogged to death: steroids have been shown, time and time again, to have no long term effect on inflammation and relapse rate in people with multiple sclerosis. Next, an unsuitable patient population is chosen: people with progressive multiple sclerosis. Thirdly, the number of participants is ridiculously low: n=30. And fourthly, an inscrutable primary outcome measure is used: the level of osteopontin in the CSF. Finally, when the primary outcome measure shows no result, the researcher claims a positive effect from significant tertiary outcome measures: in this case MRI MTR changes. Ummmmm.

ACNR prize for Confusing Antibody Data: joint between Dr Ayoglu & Dr Marignier

This is one of our most illustrious prizes, which Dr Bernard Hemmer has won several times. Every year or two, people find a serum autoantibody in people with multiple sclerosis...which then is not replicated. Dr Ayoglu and colleagues from Stockholm are old hands in this field and presented some really nice work. They had previously shown that multiple sclerosis sera contains autoantibodies to 51 antigens that are not present in healthy control sera, using antigen arrays. They now replicated this in sera from 1000 patients and controls, including controls with autoimmune disease. Their most significant finding was a high proportion of female multiple sclerosis patients have antibodies to anoctamin 2, a calcium-activated chloride channel involved in olfaction and expressed in photoreceptors. There is plenty of work to do to make sense of this discovery, but first we should see if it is replicated.

In passing, Dr Ayoglu pointed out that they had not found antibodies against the potassium channel KIR4.1, adding to the list of studies which have not confirmed Bernard Hemmer's 2012 NEJM claim that half of multiple sclerosis patients have anti-KIR4.1 antibodies. But, just when we thought that story was dead, Dr Marignier, from Lyon, popped up and showed – using a cell-based assay - poor evidence that some cases of neuromyelitis optica have antibodies against KIR-4.1. Bernard Hemmer, who was chairing the session, explained that his group are now convinced that one explanation for the discrepancy in results is the variable post-translational modification of KIR4.1 in different cell types. Rather unconvincingly, he claimed that ELISAs are better than cell-based assays. So, it looks as though this prize will continue to have many applicants in 2015.

ACNR Genetics Prize: IMSGC (Again)

We have a standing booking for the IMSGC to win this prize. They are – more or less – the only genetic show in town. Phil de Jager presented a joint analysis of "GWAS number 3" and the "MS Chip" giving sample sizes of 35,314 cases and 45,848 controls that now lead to a grand total of 159 variants with genome-wide significance, which still explains less than half of the heritability of the disease. The new pathways identified by this analysis are NK-mediated cytotoxicity and intestinal immune network of IgA production for instance, alongside what we already knew (T cell development, jak-stat activation and lots of T cell thingys). As we have come to expect, the vast majority of the variants are related to immune, mainly T cells, but curiously (because this contradicts David Hafler's summary of the same work) de Jager claimed that there are some genetic variants which are mainly expressed in brain cells. In another presentation, of the IMSGC's work on multiple sclerosis in African-Americans, seven new candidates were found of which one, called SMG7, survived a tough replication test; this RNA processing gene is also associated with lupus. This programme of work is a treasure trove for people wanting to understand the pathogenesis of multiple sclerosis.

ACNR Prize for the Most Inappropriately Written-Off Phase 3 Trial: Daclizumab

In truth this was not a good meeting for clinical trials. There was very little that was new or exciting. After the excitement of the last couple of years, I think we are in a cooling-off period. I am – apparently – alone in thinking that the results of the DECIDE trial are reasonably hopeful. Pretty much everyone I spoke to has written off daclizumab because the disability endpoint of this study failed. Daclizumab is an antibody against the IL-2 receptor and has been used in transplantation medicine for some time. It is self-administered SC once monthly and, in this trial, was compared to interferon-beta in 1841 patients. Daclizumab reduced relapse rate and new MRI lesion rate by about 50% but failed to show a significant difference on disability (EDSS changes) confirmed over 3 months. However, it did show a disability difference when confirmed over 6 months, which is traditionally considered the most robust measure of disability change. And I have learnt that phase 3 trials are fragile things, which can generate odd results. So, a sympathetic analyst looks for convergence of other outcome measures. To my mind, daclizumab's most impressive result was that it significantly reduced brain atrophy compared to that on interferon. There were some skin side effects, but not too much bother otherwise. So, I think daclizumab is probably better than the headline negative result.

The varied motor neuron disease phenotypes

Steve Vucic, MBBS, PhD
is an Associate Professor in the Faculty of Medicine, University of Sydney, Director of Neurophysiology and Consultant Neurologist at Westmead Hospital in Sydney. His major area of research interest is in the field of neurophysiology, neurodegenerative diseases, and neuroimmunology in particular assessment of cortical function in amyotrophic lateral sclerosis and multiple sclerosis.

Correspondence to:
Associate Professor Steve Vucic,
Department of Neurology,
Westmead Hospital,
Cnr Darcy and Hawkesbury Rd,
Westmead Sydney 2145, Australia
Email: s.vucic@neura.edu.au

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Summary

- MND exhibit variable phenotypes
- ALS is the commonest and most lethal of the phenotypes
- Cognitive impairment is a feature of MND

Introduction

Motor neuron disease (MND) encompasses a group of rapidly progressive and universally fatal neurodegenerative disorders of the human motor system, first described in the mid-19th century by the French Neurologist Jean Martin Charcot.[1] Amyotrophic lateral sclerosis (ALS) is the commonest MND phenotype, clinically characterised by progressive neurological deterioration and co-existence of upper and lower motor neuron signs.[2] In addition, the varied clinical presentations of MND also include (i) progressive muscle atrophy (PMA, ~ 10% of MND cases), a clinically pure lower motor neuron (LMN) phenotype, (ii) primary lateral sclerosis (PLS, 1-3% of MND cases), a clinically pure upper motor neuron (UMN) phenotype and (iii) progressive bulbar palsy (PBP, 1-2% of MND cases), an isolated bulbar phenotype with relative preservation of spinal motor neurons. More recently, an association between ALS and frontotemporal degeneration (FTD) has been established, suggesting that ALS forms a continuum with primary neurodegenerative disorders, a notion underscored by the identification of the c9orf72 hexanucleotide expansion.[3,4] Despite the clinical heterogeneity, median survival of MND remains three years, although the atypical phenotypes exhibit a longer survival.[5]

Amyotrophic lateral sclerosis

In European-based population studies the incidence of ALS appears uniform at 2.16 per 100,000 person-years with a prevalence of 4-6 per 100,000,[6] with a lifetime risk of developing ALS being 1 in 400, where the incidence is slightly higher in males [1.2-1.5:1].[6] Sporadic ALS peaks between the ages of 50 to 75 years and declines after the age of 80,[5] with the age-specific incidence remaining stable over the past decade.[7] The frequency of ALS is significantly lower in non-Caucasian populations,[8] suggesting a role for genetic factors in ALS susceptibility. A genetic aetiology has been identified in up to 20% of apparently "sporadic" and 60% of familial ALS cases, in which two or more family members are clinically affected, with at least 16 genes and genetic loci implicated in ALS pathogenesis.[9]

Clinically, ALS is characterised by co-existence of upper and lower motor neuron signs encompassing multiple body regions, with evidence of progressive deterioration.[2] Lower motor neuron signs are clinically characterised by fasciculations, muscle wasting and weakness, while UMN signs include slowness of movement, increased tone, hyper-reflexia and extensor plantar responses. The majority of ALS patients present with limb-onset disease (65-75%),[10] spreading along the neuraxis to affect contiguous motor neurons.[11,12] Preferential wasting and weakness of thenar muscles, termed the split-hand phenomenon (Figure 1), is a specific feature of ALS.[13,14] While fasciculations are a cardinal feature of ALS, they are infrequently the presenting symptom.[15] Patients presenting solely with fasciculations and muscle cramping should be monitored as these may infrequently progress to develop ALS.[16] Extra-ocular and sphincter muscles are preserved until advanced stages of the disease,[17] and sensory nerves are not typically affected.[5]

Bulbar-onset disease may be evident in 20-25% of patients, characterised by progressive dysarthria, dysphagia, hoarseness, tongue wasting, weakness and fasciculations as well as emotional lability.[2] Aspiration pneumonia, malnutrition and weight loss are consequent features resulting in an adverse prognosis.[18] Respiratory dysfunction is a late feature of ALS, ultimately resulting in terminal respiratory failure,[19] although rarely may be the presenting symptom.[20,21]

The "split hand" sign refers to preferential wasting of the thenar group of muscles, including the abductor pollicis brevis (APB) and first dorsal interosseous (FDI), when compared to the abductor digit minimi (ADM) [Figure 1].[14,22] This pattern of muscle atrophy is specific for ALS, and may differentiate ALS from potential mimic disorders.[13] The ability to quantify the split hand sign, through the development of a split-hand index (SI), was recently demonstrated to be of diagnostic significance in ALS.[23] The mechanisms underlying the split hand in ALS remain elusive, although cortical hyperexcitability seems to be most plausible mechanism.[23]

In addition to pure motor symptoms, subtle cognitive abnormalities may be evident in up to 50% of ALS patients,[24] characterised by executive dysfunction, language and memory impairment along with behavioural abnormalities, which may precede the onset of motor symptoms.[24] Recognition of cognitive dysfunction has implication for vital management of ALS, as these symptoms may adversely impact on patient compliance and decision-making abilities. At the extreme end of the spectrum, frontotemporal dementia may develop in up to 15% of ALS patients,[6,24] and is clinically characterised by executive and language dysfunction, irrational behavioural, personality changes, apathy, poor insight, loss of empathy, irritability and disinhibition.[25]

The presence of psychiatric features in the setting of FTD-ALS may be indicative of a recently discovered genetic mutation in the c9orf72 gene on

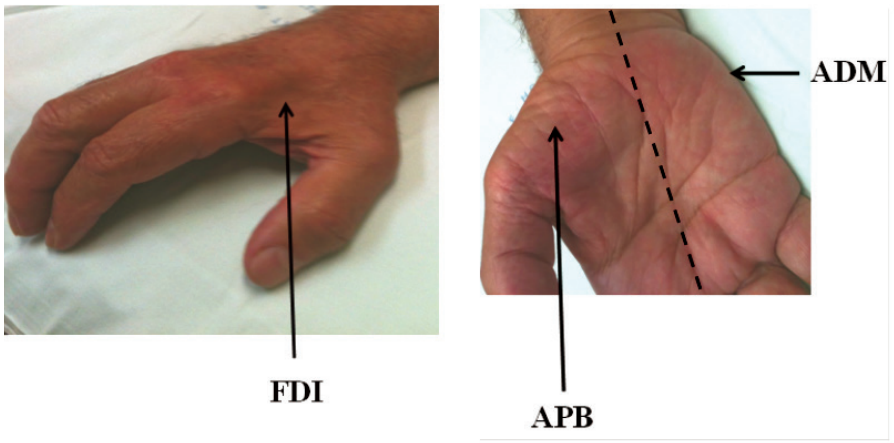

Figure 1: Split hand index refers to preferential wasting of first dorsal interosseous (FDI) and abductor pollicis brevis (APB) with relative preservation of the abductor digit minimi (ADM) muscle.

Table 1: Amyotrophic lateral sclerosis patients present with a combination of upper and lower motor neuron signs.

UPPER MOTOR NEURON SIGNS	LOWER MOTOR NEURON SIGNS
Increased tone	Muscle Wasting
Hyper-reflexia	Weakness
Extensor plantar responses	Fasciculations
Spastic gait	Absent or reduced deep tendon reflexes
Exaggerated jaw-jerk	
Slowed movements	

chromosome 9p21.[25] Specifically, increased hexanucleotide repeat expansion (GGGGCC) in the intornic segment of the c9orf72 gene, which appears to be dominantly inherited, is causative for both ALS and frontotemporal dementia.[3,4] Importantly, the c9orf72 hexanucleotide expansion appeared to underlie over 40% of familial and 20% of sporadic ALS cases in the original studies,[3,4] although subsequent studies have established a frequency of 4.1-8.3% in apparently "sporadic" ALS cohorts.[26] In addition to predisposition for dementia, the c9orf72 ALS cohorts exhibit an earlier age of onset and shorter survival.[27] The c9orf72 discovery has radically altered the understanding of ALS pathogenesis, implying that ALS is a multisystem neurodegenerative disorder, rather than a pure neuromuscular disease.[9] Importantly, accumulation of TDP-43 along with p62 positive TDP-43 negative inclusions in hippocampus and cerebellar neurons appears to be neuropathological hallmarks of c9orf72 associated ALS and FTD,[28] suggesting the existence of a common pathophysiological pathway, although the precise pathophysiological mechanisms appear to be complex and remain to be fully elucidated.[29]

The diagnosis of ALS remains clinically based relying on identifying a combination of UMN and LMN signs, with evidence of disease progression.[30] Nerve conduction studies (NCS) and electromyography (EMG) are important clinical investigations, excluding potential mimic disorders,[2] and identifying widespread LMN dysfunction, a cardinal feature of ALS. Specifically, LMN dysfunction may be heralded by the presence of ongoing activity (fibrillation potentials and positive sharp waves) and chronic neurogenic changes (large-amplitude, long-duration, polyphasic motor unit potentials), and if widespread appear to exhibit a high sensitivity and specificity for ALS.[31] Importantly, the EMG changes may be evident sub-clinically, thereby enabling an earlier diagnosis of ALS.[32] In addition, widespread fasciculations with a high firing frequency and increased frequency of double fasciculations, may also be a diagnostic feature of ALS,[33] especially when combined with clinical features and disease progression.

Atypical MND phenotypes

Atypical MND phenotypes include progressive muscular atrophy, the clinically "pure" lower motor neuron phenotype, encompassing the flail-arm and some of the flail leg variants. The flail-limb variants are characterised by neurogenic weakness confined to the proximal upper limbs (flail-arm, at least for 24 months) or lower limbs (flail-leg, confined to lower limbs for at least 12 months).[34,35] Importantly, one-third of PMA cases may develop UMN dysfunction, and while the overall prognosis for the flail-arm and leg variants is favourable,[35] a progressive course akin to that evident in ALS may also be evident in PMA,[36] underscoring the notion that PMA falls into the spectrum of MND diseases.

Of further relevance, primary lateral sclerosis refers to the pure UMN phenotype, characterised by a slowly progressive UMN syndrome (Table 1) affecting the spinal and bulbar regions with relative preservation of the lower motor neurons for at least four years after symptom onset.[37,38] Importantly, lower motor neuron signs may develop within four years of symptom onset, and this group is then classified as upper motor neuron predominant-ALS.[38] The PBP phenotype remains localised within the bulbar region for a prolonged period (>6 months) and is characterised by female predominance and UMN bulbar dysfunction, although clinical features of ALS may develop.[39] The rates of survival for the UMN phenotypes of MND are typically prolonged, although significant functional impairment occurs.[29]

In conclusion, MND appears to be a clinically heterogeneous disorder with varied clinical presentation encompassing a range of upper and lower motor neuron dysfunction. The overlap in clinical features, along with evidence of disease progression underscores the notion that common pathophysiological processes underlie varied MND phenotypes. Discovering the processes that regulate the development of the varied clinical phenotypes, may yet result in development of adequate therapeutic strategies.

Table 2: Motor neuron disease (MND) may exhibit varied phenotypes.

MND phenotypes	Upper motor neuron features	Lower motor neuron features	Prognosis
Amyotrophic lateral sclerosis	Yes	Yes	Poor (Median survival 3-5 years)
Primary lateral sclerosis	Yes	No	Good (Survival › 5 years)
Progressive muscular atrophy – Flail arm variant ALS – Flail leg variant	Subclinical Clinical in 30%	Yes	Variable
ALS-frontotemporal dementia	Yes	Yes	Poor – Test for c9orf72 gene

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Brain researcher, John O'Keefe, wins Nobel Prize

John O'Keefe, Professor of Cognitive Neuroscience at University College London, has been jointly awarded the 2014 Nobel Prize in Medicine for helping to uncover the brain's "inner GPS system."

Professor O'Keefe made the first key discovery in understanding the brain's navigation system in 1971 when he identified "place cells" which map the environment around us. His research into how the healthy brain functions, especially areas of the brain crucial to learning and memory, has provided a greater understanding into what changes occur during conditions such as Alzheimer's disease.

Professor O'Keefe was awarded the most prestigious prize in science alongside Norwegian researchers May-Britt Moser and Edvard Moser.

Howard Knox
(1885-1949): a pioneer of neuropsychological testing

Tom Kelly
is the Clinical Lead for Neuropsychology in Newcastle Hospitals NHS Foundation Trust. He works in the area of acquired brain injury with adults and children. He runs a Cognitive Clinic with a neurology colleague Professor Tim Griffiths.

AJ Larner
Cognitive Function Clinic,
Walton Centre for
Neurology and Neurosurgery.

Correspondence to:
AJ Larner,
Walton Centre for Neurology
and Neurosurgery,
Lower Lane,
Fazakerley,
Liverpool L9 7LJ, UK.
Email: a.larner@
thewaltoncentre.nhs.uk

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Figure 1: Knox (centre) apparently undertaking performance testing with a recently arrived immigrant at Ellis Island

Many visitors to New York will take the brief ferry trip from Battery Park to Liberty Island to see the Statue of Liberty (or "Liberty Enlightening the World" as Frédéric Auguste Bartholdi's monumental sculpture was originally called), and may then travel on to Ellis Island where many immigrants to the United States of America first arrived in the early 20th century.

Viewing the exhibits in the Ellis Island Immigration Museum, the visitor, particularly if from a neuroscience background, may be startled to come across early 20th century photographs of newly arrived immigrants being subjected to neuropsychological testing (Figure 1), and thus may encounter for the first time the work of the physician Howard Andrew Knox (1885-1949). This may prompt the curious visitor to seek more information on this little known and largely neglected figure in the history of neuropsychology, neglected that is until the work of John Richardson to which we are indebted for a vivid portrayal of the man, his work, and times.[1,2]

Knox worked as an assistant surgeon for the US Public Health Service at Ellis Island for just four years (May 1912-May1916). Then (as now) anxieties about immigration were prevalent, particularly the risk of large numbers of immigrants with "mental deficiency" being unable to work and hence becoming dependent on the public purse, along with the concerns of the eugenics movement that this would impoverish the racial stock of the country (mental deficiency was viewed at this time as a largely inherited trait). Ellis Island represented a front line for the identification of such immigrants, and their deportation back to their countries of origin (mostly in eastern and southern Europe). But how could such individuals be reliably identified among the mass of people arriving on a daily basis in the voluminous Ellis Island "hall of judgement"?

Along with colleagues at Ellis Island, Knox developed and popularised a number of tests which may be characterised as tests of performance, being one of the first to use this phrase to describe overt non-verbal behaviour. Tests existing at that time, such as the scale of Binet and Simon, assumed a particular culture and language that rendered them entirely unsuitable for use with the immigrants arriving at Ellis Island. It was recognised that new tests should as far as possible eliminate the language element and cultural knowledge, or in other words should be culture-free or, since this may not be possible, culture-fair. Richardson (ref 2, p 256) identifies Knox as the first proponent of such culture-fair tests.

Knox developed over a dozen tests over a short

period of time, such as the Cube Imitation Test and the Feature Profile Test, as well as dabbling with ink blots (Inkblot Imagination Test) independently of Rohrschach, with whom they are more commonly associated. The purpose of the tests would be immediately familiar to any current neuropsychologist, for example the Cube Imitation Test is very similar to the visual working memory tests, such as that in the Wechsler Memory Scales 3rd Edition.[3] Knox popularised his tests in over a dozen publications, including high profile journals such as the *Journal of the American Medical Association*[4] and *Scientific American*.[5] The latter article, now nearly a century old, represents one of the first attempts to explain a cognitive test battery to a broader scientific audience. Knox believed these constituted a graduated system of accurately standardised performance tests of increasing complexity suited to patient age, education and previous environment. Although none of Knox's tests remains in use today, performance testing is still an integral part of neuropsychological assessment, as enshrined in the performance IQ component which was part of the Wechsler Adult Intelligence Scale up to the publication of the fourth edition of these scales in 2008.[6]

Besides the nature of the tests themselves, Knox was also alert to the issue of the test environment. Imagine that you have left your home, travelled thousands of miles by ship over a period of 10 days or so, perhaps in cramped and unsanitary conditions, with inadequate food and sleep, facing a future shrouded in uncertainty, and upon arrival at your destination you are then required to undertake some form of testing procedure which is entirely alien to the way of life and habits of thought which are familiar to you. Will your performance on such tests be optimal? Almost certainly not. Knox recognised the need for rest, adequate nutrition, sleep, a quiet and well-ventilated testing room, freedom from other distractions, as well as a sympathetic examiner and interpreter, for optimal test performance. He suggested that immigrants who failed initial testing should be given a second opportunity on subsequent days.[5]

Some of the issues which Knox tried to address remain with us today, specifically issues around language and culture, and test environment. Testing individuals in the cognitive clinic may be difficult if English is not their first language, hence the need for translation of many commonly used cognitive screening instruments, such as the Addenbrooke's Cognitive Examination and its iterations[7] and the Montreal Cognitive Assessment (see www.mocatest.org), into different languages. Knox understood the need not only to translate items but to develop different normative data for different cultural groups, something which is still lacking in many of our standard neuropsychological batteries a hundred years later. A number of cognitive screening instruments are claimed, sometimes on the basis of cultural modification and cross-cultural testing, to be culture-fair, such as the Clock Drawing Test, the Mini-Cog, the 7-minute screening battery, and the Time and Change test.[8] It is now probably accepted by most neuropsychologists that whilst testing can be language free it cannot be culture free.

As for test environment, clinic rooms pervaded by extraneous noise (radio, television) and liable to interruption (passing outpatient department assistants, medical students) are still inappropriately assigned for cognitive clinics, sometimes for lack of more suitable accommodation. The problems which Knox faced 100 years ago are still likely to be with us in future years.

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To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th December, 2014

November

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact info@redpublish.co.uk

Managing Patients' Cognitive Impairment
Thurs 10th Nov, The 52 Club, Gower St, London WC1E. Cost £135
www.communitytherapy.org.uk/events.html
E. info@communitytherapy.org.uk

22nd Annual Meeting of the European Charcot Foundation
November 20-22, 2014;Baveno, Italy
www.charcot-ms.org

December

Encephalitis: A Global Perspective of Outcomes
1 December 2014; London, UK
T. 01653 692583, E. admin@encephalitis.info.
Places are FREE for our Professional Members.

Multiple Sclerosis 2014
3 December, 2014; London, UK
www.mahealthcareevents.co.uk/MS2014

Sleep Disorders and Fatigue in Neurology
5th December, 2014; Raphael Medical Centre, Tonbridge, Kent.
www.communitytherapy.org.uk/events.html
E. info@communitytherapy.org.uk

2015

February

Dementias 2015
5-6 February, 2015; London, UK
www.mahealthcareevents.co.uk/dementias2015

March

National Brain Injury Symposium: complexity & Best Practice
13 March, 2015; London, UK
T. 0208 780 4500 x5140, E. institute@rhn.org.uk

May

ABN Annual Meeting
19-22 May, 2015; Harrogate, UK
E. info@theabn.org

June

Consultant PD Masterclass – Sheffield, UK
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

1st Congress of the European Academy of Neurology
20-23 June, 2015; Berlin, Germany
E. headoffice@eaneurology.org

Consultant PD Masterclass – Sheffield
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

September

Registrar PD Masterclass –
16/17th September, 2015; Sheffield, UK
www.parkinsonsacademy.co.uk for further details.

Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information. COPAXONE® (glatiramer acetate) 20 mg/ml Solution for Injection, Pre-filled Syringe Abbreviated Prescribing Information Presentation: Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indications:** Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration:** 20mg of glatiramer acetate subcutaneously once daily. It is not known for how long the patient should be treated. A decision concerning long term treatment should be made on an individual basis by the treating physician. *Adolescents (12 - 18 years):* No specific studies. Limited published data suggest the safety profile of 20mg administered subcutaneously once daily is similar to that seen in adults. *Children (<12 years):* Not recommended. *Elderly:* No specific data. *Impaired renal function:* No specific studies. Monitor renal function during treatment and consider possibility of glomerular deposition of immune complexes. **Contraindications:** Known allergy to glatiramer acetate or mannitol. Pregnancy. **Precautions and warnings:** Subcutaneous use only. Initiation to be supervised by neurologist or experienced MS physician. Instruct patients in self injection technique and supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, serious hypersensitivity reactions may occur. If severe, treat appropriately and discontinue Copaxone. **Interactions:** No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation:** Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Effects on ability to drive and use machines:** No studies have been performed. **Adverse reactions:** *Very Common:* Infection, influenza, anxiety, depression, headache, vasodilatation, dyspnoea, nausea, rash, arthralgia, back pain asthenia, chest pain, injection site reactions, pain. *Common:* Bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis, benign neoplasm of skin, neoplasm, lymphadenopathy, hypersensitivity, anorexia, weight increased, nervousness, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor, diplopia, eye disorder, ear disorder, palpitations, tachycardia, cough, rhinitis seasonal, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, faecal incontinence, vomiting, liver function test abnormal, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, neck pain, micturition urgency, pollakiuria, urinary retention, chills, face oedema, injection site atrophy, local reaction, oedema peripheral, oedema, pyrexia. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted. Price: 28 pre-filled syringes of Copaxone: £513.95. **Legal category:** POM. **Marketing Authorisation Number:** 10921/0023 **Marketing Authorisation Holder:** Teva Pharmaceuticals Ltd, Ridings Point, Whistler Drive, Castleford, West Yorkshire. WF10 5HX. United Kingdom. **Date of preparation:** June 2013
Job Code: UK/MED/13/0034

Date of preparation: October 2013 **Job code:** UK/CPX/13/0008l

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