

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Siddharthan Chandran and Andrea Serio

– The Use of Stem Cells in Motor Neurone Disease (MND)

NEW SERIES

Neuro-Ophthalmology – Patrick Yu-Wai-Man and Patrick F Chinnery

– Leber Hereditary Optic Neuropathy – Therapeutic Challenges and Early Promise

Controversies in Neurology – Sivakumar Sathasivam,

– Ethical Considerations in Physician-Assisted Suicide

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Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food and with or without levodopa. **Elderly:** No change in dosage required. **Children and adolescents** (<18 years): Not recommended. **Patients with renal impairment:** No change in dosage required. **Patients with hepatic impairment:** Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. **Overdose:** Symptoms reported following rasagiline overdose (3-100mg) included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic impairment. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and MAO inhibitors. Cases of serotonin

syndrome have been reported post-marketing in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including rare cases of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident,

angina pectoris. Please refer to the SmPC for the rates of adverse events. **Basic NHS Price:** Azilect® (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** September 2010. **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

References:

1. Azilect Summary of Product Characteristics. October 2010.
2. Stocchi F, Brooks DJ, Melamed E et al. Effects of rasagiline on severity of OFF in Parkinson's disease. Poster presented at the 58th American Academy of Neurology Annual Meeting, San Diego, California, USA. 2006.

Job No. UK/AZI/1107/0152 AZT/0711/0024
Date of preparation: July 2011

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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. He is currently secretary for the ABN trainees committee.



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Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

ECTRIMS Research Exchange Programme

This fellowship is offered to young European postdoctoral neuroscientists (MD, PhD, ScD or equivalent) to facilitate their conduct of and training in basic, clinical or applied research related to MS in European laboratories or clinics. The goal is to maximise exchange of information and help grow the pool of well-trained scientists focused on MS. ECTRIMS will support up to two fellowships annually, each with duration of one or two years, with an annual stipend of up to €40,000 - €50,000, depending on the candidate's degree. Fellows are expected to identify a European research training environment and mentor prior to application and to devote full-time to research and research training during their fellowship period (up to 10% time and effort can be spent on teaching and/or clinical care).

For more information see www.ectrims.eu or E.fellowship@ectrims.eu

Funding for Neurodegenerative disease research projects

Professor Martin Rossor and Professor Anthony Schapira have both been awarded funding in the first ever Centres of Excellence in Neurodegeneration Research (CoEN) initiative. CoEN, an international collaborative of research funders including the UK's Medical Research Council, launched the initiative last year, with a remit of bringing together researchers from labs across the globe to further understanding of neurodegenerative diseases and identify new ways of treating these diseases.

Age-associated neurodegenerative diseases are complex and little is known about what causes them. Furthermore, according to WHO, they are estimated to become the second leading cause of death after cardiovascular disease by 2040. Researchers must create a common research language across all neurodegenerative pre-clinical, clinical and population-based studies. The CoEN initiative, which builds on research already taking place at recognised centres of excellence (CoE) in neurodegeneration and increases collaborative activity between researchers, hopes to do just that, by promoting better integration in neurodegenerative research.

Professor Rossor and Schapira's collaborative projects are two of eight such projects funded by the CoEN initiative.

For more information see <http://coen.org/home.html>



Royal Society of Medicine Clinical Neurosciences Section President's prize

Applicants are invited to submit an anonymous one A4 page (up to 250 words) summary of a clinical paper on an interesting case or case series. Applicants name and the name of the institution should not be mentioned or included in the text.

A maximum of five papers will be selected for oral presentation at the meeting on 1st March 2012. Presentations will be 10 minutes long followed by a 5-minute discussion. A panel of judges will determine the best presentation and the President's Prize of £300 will be awarded at the end of the meeting.

Submission Deadline January 19th, 2012. Open to trainees in all areas of clinical neurosciences, including neurology, neurosurgery, neurophysiology, neuropathology or neuroradiology.

For more information E.cns@rsm.ac.uk

New – Gilenya an MS treatment that's oral

Prior IFN treatment

Failed response
to full and
adequate course



Relapse

Unchanged or
increased rate, or
ongoing severe
relapses



Prescribe Gilenya

Once daily
oral MS therapy



Abbreviated Prescribing Information: GILENYA® (fingolimod)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC). **Presentation:** Hard capsule containing 0.5 mg fingolimod (as hydrochloride). **Indications:** Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. **Dosage: Adults:** Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta-interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. **Safety and efficacy of Gilenya in children up to 18 years has not been established. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. Contraindications:** Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any

of the excipients. **Warnings/Precautions: Bradycardia:** Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays. Observe all patients for 6 hours for bradycardia. In the event of bradycardia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya has not been studied in patients with sitting heart rate <55 beats per minute, second degree or higher AV block, sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure, significant cardiovascular disease, a history of syncope or those taking beta blockers. Seek advice from a cardiologist before initiation of treatment in these patients. Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Exercise caution at treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate (e.g. verapamil, digoxin, anticholinesteratic agents or pilocarpine) due to possible additive effects. Avoid medicinal products that may prolong QTc interval. **Infections:** Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline, and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count <0.2x10⁹/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. **Macular oedema:** Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. **Liver function:** Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3 and 6 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum



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A new perspective in MS

bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. **Serological testing:** Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. **Blood pressure effects:** Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. **Respiratory effects:** Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV₁) and diffusion capacity for carbon monoxide (DLCO). **Prior immunosuppressant treatment:** No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. **Stopping therapy:** Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system. **Interactions:** Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, exercise caution when initiating Gilenya in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine. Caution is indicated with substances that may

inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod. **Fertility, pregnancy and lactation:** There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility. **Undesirable effects:** *Very common* ($\geq 1/10$): Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common* ($\geq 1/100$ to $< 1/10$): herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, paraesthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): pneumonia, macular oedema, decreased neutrophil count. **Packs and price:** Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK. **Marketing Authorisation Numbers:** 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005 **Date of last revision of prescribing information:** March 2011. **Full Prescribing Information available from:** Novartis Pharmaceuticals UK LTD, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Novartis (01276) 698370

Date of preparation: March 2011 Code: FIN11-102

The prognosis in Motor Neurone Disease (MND) is poor and so any approach that offers any therapeutic hope needs to be explored. In their review Siddharthan Chandran and Andrea Serio discuss how this might be possible using stem cells. They make the point that the discussion on stem cells in MND should not be limited to cell replacement but rather we should be thinking of them as a therapy that could support diseased cells. In addition, the advent of reprogramming technology (see also Journal reviews) makes the prospect of looking at a relevant disease process in vitro one step closer.

Whilst the possibilities of using stem cells for treating MND is an exciting one, at the other end of the spectrum is the desire by some patients with this condition to end their life. In this respect, the discussion around Physician Assisted Suicide (PAS) has become a topic of great debate and controversy. In this issue of the ACNR, Dr Sivakumar Sathasivam discusses this area of debate, initially from a philosophical perspective before ending up in the modern day and what this means for patient and doctor choices. In response our very own Co-editor, Dr Alasdair Coles, gives his thoughts on this article and how the implications of what is being discussed plays out in clinical practice. If you would like to contribute to this debate then please do.

The article in our Leading Norwegian Neuroscience Discoveries series is from Laurence Bindoff and Charalapos Tzoulis and discusses their seminal work on POLG gene abnormalities as a major cause of mitochondrial disease in adults. In this short review they discuss how their work began and has evolved and where it is now heading.

Continuing on this theme of mitochondrial disease, Patrick Yu-Wai-Man and Patrick Chinnery in the first of our Neuro-ophthalmology series discuss Lebers Hereditary Optic Neuropathy (LHON). This article not only discusses the clinical features and genetic basis for this condition but reports on a recent trial (the RHODOS trial) using idebenone as a treatment with encouraging results.

Intraventricular haemorrhage in premature babies is still a major problem. In his article, Kristian Aquilina discusses this whole issue from pathophysiology to best management and en route highlights some of the problems that arise. This superb review is a really useful guide to a major problem and serves to illustrate how better understanding this disorder has led to better management.

Should one use anti-depressants in patients with epilepsy? There is often great confusion about this and this can lead to tensions between those seeing the patients in hospital clinics, who recommend such treatments, and GPs who are often worried about doing this for fear of worsening their seizures. John Mellers in his article for the Clinical dilemmas in Neuropsychiatry explains where the truth lies and concludes that the evidence that anti-depressants are dangerous in epilepsy is not very compelling.

Anna Maw in her article in the Paediatric Neurology series takes us through a study she has undertaken on head injury in children. This study highlights some of the problems in the long term of those affected by this type of injury, especially those in whom the head injury is mild.

What is the best way to manage patients with chronic neurological disorders in a health care system where the emphasis is on seeing new cases not follow ups? Tarek Gaber and Janet Priest in their contribution to the Rehabilitation series take us through the processes that underlay the reconfiguration of their local services and how this has impacted on improved quality of care across the board.

As always we have our usual series of conference reports, book reviews and journal highlights that we hope you will enjoy. ♦



Roger Barker, Co-Editor.

*Roger Barker, Co-Editor,
Email. Rachael@acnr.co.uk*

Life with epilepsy can be much more
than just a gap between seizures

It's hard to live life to the full if part of you is always expecting the next seizure. VIMPAT® is an anti-epileptic drug with an innovative mode of action.^{1,2} In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.³ Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.^{1,3}

VIMPAT®
lacosamide

Confidence, when monotherapy is not enough

PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing). **Vimpat® Lacosamide Active Ingredient:** Tablets: lacosamide 50 mg, 100 mg, 150 mg and 200 mg. **Solution for infusion:** lacosamide 10 mg/ml. **Indication:** Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** Adults and adolescents from 16 years: Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). **For solution for infusion:** Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. **Elderly:** No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. **Paediatric patients:** Not recommended. **Patients with renal impairment:** No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended for patients with severe renal impairment and patients with end-stage renal disease (see SPC). Dose titration should be performed with caution. **Patients with hepatic impairment:** No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if Vimpat has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings, etc:** **Contraindications:** Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. **Precautions:** Lacosamide has been associated with dizziness. Use with caution in patients with

known conduction problems, severe cardiac disease or in elderly. Second degree or higher AV block has been reported in post-marketing experience. Atrial fibrillation or flutter have been reported in open-label trials and in post-marketing experience. Patients should be made aware of the symptoms of second-degree or higher AV block and of the symptoms of atrial fibrillation and flutter. Patients should be counseled to seek medical advice should any of these symptoms occur. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, confusional state, insomnia, balance disorder, abnormal coordination, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, hypoesthesia, dysarthria, disturbance in attention, blurred vision, vertigo, tinnitus, vomiting, constipation, flatulence, dyspepsia, dry mouth, pruritus, rash, muscle spasms, gait disturbance, asthenia,

fatigue, irritability, injection site pain or discomfort, irritation, fall, skin laceration. The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR prolongation may occur. Please consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. **Solution for infusion:** Do not store above 25°C. Use immediately. **Legal Category:** POM. **Marketing Authorisation Number(s):** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; **Solution for Infusion (10 mg/ml) x 20 ml:** EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 200 mg x 56 tabs: £144.16; **Solution for Infusion (10 mg/ml) x 20 ml:** £29.70. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 08/2011 (UK/11VPE0111a). Vimpat is a registered trademark.

References:

1. Vimpat Summary of Product Characteristics.
2. Beyreuther BK et al. CNS Drug Rev 2007; **13**(1): 21-42.
3. Chung S et al. CNS Drugs 2010; **24**(12): 1041-1054.

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Cover picture: Courtesy of Nikon Small World competition. Image of distinction: Primary rat neurons grown as neurospheres, by Dr Rowan Orme, Keele University, Keele, UK.

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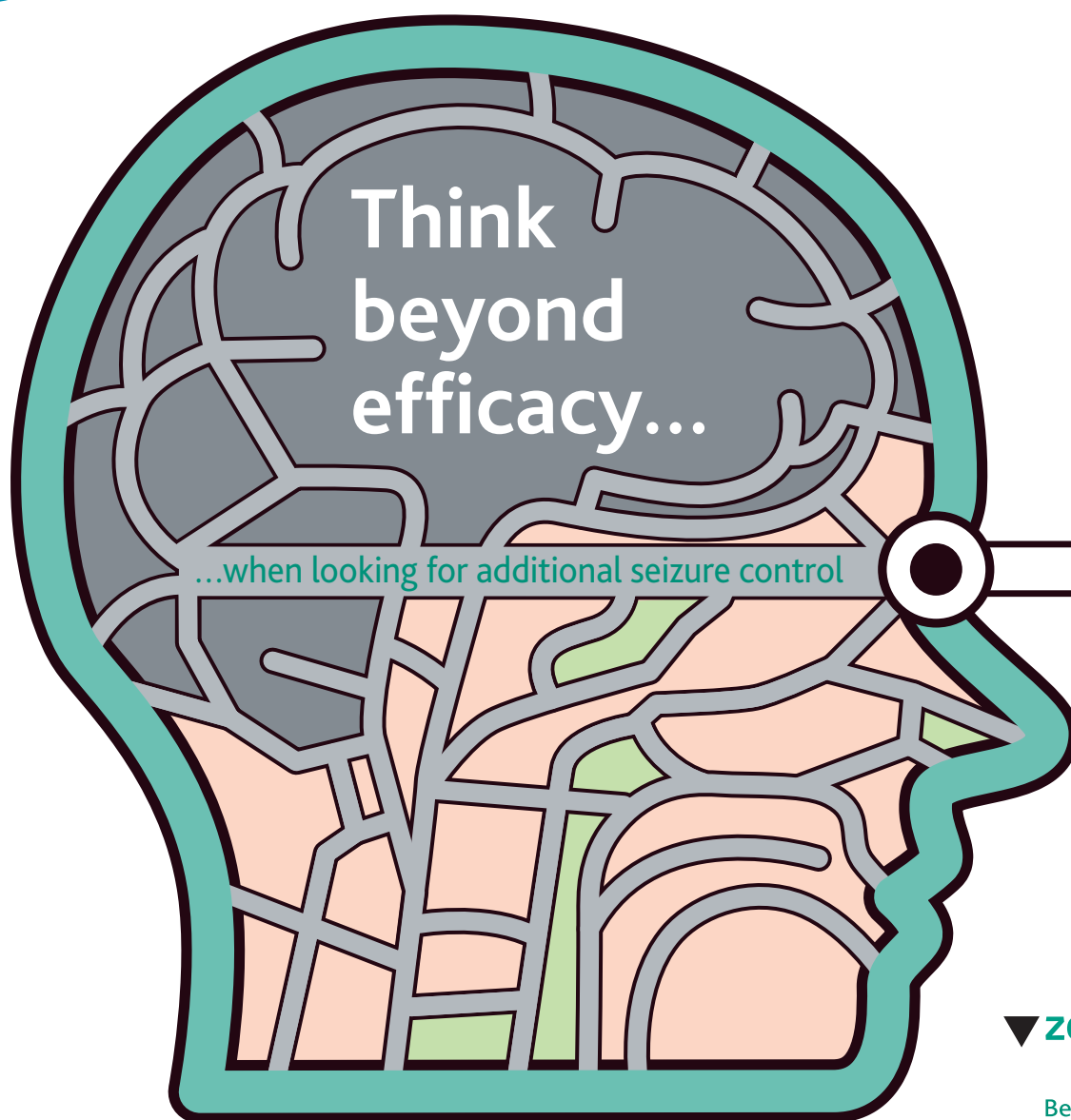
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Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

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somnolence, diplopia, decreased bicarbonate. Common effects ($\geq 1/100$, $< 1/10$): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, urinary calculus. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥ 65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal Category:** POM. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. **Marketing authorisation numbers:** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. **Marketing authorisation holder:** Eisai Ltd. **Further information from/marketed by:** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. **Date of preparation:** July 2011.

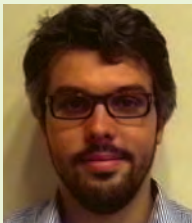
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The Use of Stem Cells in Motor Neurone Disease (MND)



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Motor neurone disease (MND) or amyotrophic lateral sclerosis (ALS) is a fatal late onset neurodegenerative disorder that results in progressive and selective degeneration of motor neurones (MNs) through poorly understood mechanisms.^{1,2} At present there is a lack of therapies that can significantly alter the course of ALS, and usually death occurs within three years from symptom onset due to respiratory failure.

MND is a relatively rare neurodegenerative condition with an annual incidence of 2.0-2.5 per 100,000 in the European population. The majority of cases are sporadic (sALS), but 5-10% of all cases present an inherited form of the disease (familial ALS, fALS). Following the discovery in 1993 that SOD1 mutations are associated with fALS³ a growing number of genes have been associated with inherited forms of this disease. One of the most significant is TARDBP, which encodes the protein TDP-43. This protein is involved in splicing regulation and mRNA biogenesis and has been recently shown to be a key protein in MND. TDP-43 related pathology is present in the vast majority of ALS cases⁴; with the exception of SOD1 and FUS related fALS, all other cases of this disease present mislocalisation and accumulations of ubiquitinated TDP-43.

Studying familial ALS particularly SOD1 mutations has been highly influential to our understanding of disease pathogenesis. One such insight has been the recognition of the importance of non-cell autonomous mechanisms of neurodegeneration. Specifically, the glial environment (in particular astrocytes and microglia) is thought to be central to disease progression.⁵ In turn, this has led conceptually to novel approaches to neuroprotection, including cell based approaches to manipulate the 'hostile' glial environment.

Against this background stem cell based approaches, focussing on forms of fALS, are increasingly attractive as a platform for developing, both models and potential treatments for MND.

Stem cells

Stem cells are found in all multicellular organisms and can be defined by two key properties: 1. the ability to self renew, and 2. the ability to differentiate into a range of specialised cell types according to their potency. Potency ranges from pluripotent stem cells, such as embryonic stem cells, that are able to generate every cell type in the organism to multipotent tissue specific stem cells that are able to generate those cell types that make up the tissue of origin. For example, neural stem cells can generate the neurones, astrocytes and myelinating cells that form our nervous system.

Since the discovery of reprogramming technologies in 2007,⁶ it is also possible to generate artificially induced pluripotent cells (iPS) from adult cells, for example skin fibroblasts. The basic idea behind this advance is the introduction of two to

four key 'reprogramming' factors to 'reset' the cellular machinery from an adult cell to an embryonic-like pluripotent cell. The practical implication of this technology is the increasingly widespread availability of patient specific stem cells for research or potentially treatment.

Combining these ideas with advances in human stem cell biology and new methods to generate region specific functional neurones, including MNs, and glial cells offers much promise for regenerative neurology. The absence of treatments and the appalling prognosis of MND has led to MND being considered an appropriate candidate disease for innovative experimental medicine. One of these approaches is the use of stem cells.

Using stem cells to treat MND

Conceptually cell based therapies can be categorised based on the putative mechanism of efficacy. In broad terms this can be 1. cell replacement and 2. using stem cell not to replace cells or tissue but rather to manipulate the environment around the injured or dying neurones (Figure 1).

Cell replacement, conceptually straight-forward, seeks to replace dying or lost cells with ex vivo generated cell specific progenitor(s). Aside from the challenges of immune-rejection, the basic biology to restore connectivity in the context of an adult and scarred environment remains poorly understood. In contrast to Parkinson's disease, where the key cell loss is specific to a restricted area in the midbrain, loss of MNs is extensive, ranging from cortical upper MNs to lower MNs: for this reason a successful replacement therapy would require transplanted MN progenitors to integrate into a pre-existing network. Although it is now possible to generate functional motor neurones by using protocols based on neurodevelopmental insights^{7,8} for the reasons discussed above it is presently unrealistic to use stem cells to replace MNs in MND patients. Notwithstanding this major challenge to clinical human application, it is of interest that experimental studies involving transplantation of stem cells or differentiating MNs into animal models of MND have been reported. These studies have been valuable in understanding the potential of stem cell transplantation in MND, and viewed collectively some general conclusions can be drawn: 1. the majority of studies use models of SOD1 fALS which might not necessarily be the most relevant form of the disease in humans; 2. in many cases the onset of the disease and/or the symptoms observed in the animal models is different from that observed in humans⁹; 3. stem cell transplantation is often performed before the manifestation of clinical signs, which is at variance with the clinical scenario; 4. in those stem cell transplantation studies in which amelioration of the phenotype was observed, there is little evidence that this effect was due to replacement of lost MNs in the pre-existing neuronal network¹⁰; 5. increasing evidence suggests that the functional recovery

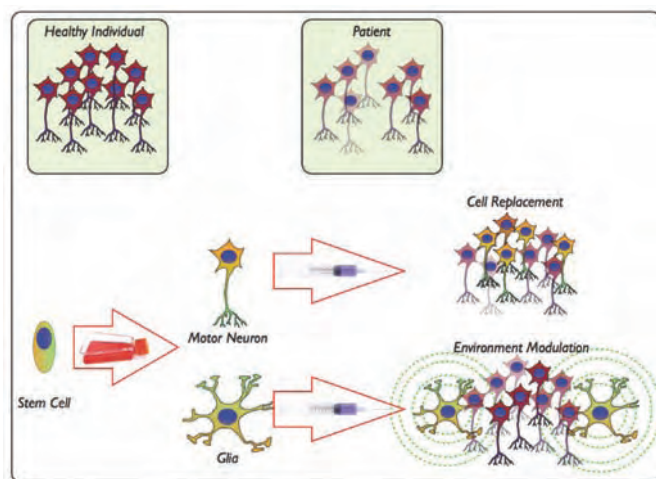


Figure 1: Stem cell therapies can be categorised into cell replacement or indirectly beneficial through environment modulation. In the case of ALS, direct in vitro differentiation of stem cells into motor neurons or glial cell types could be used for both approaches.

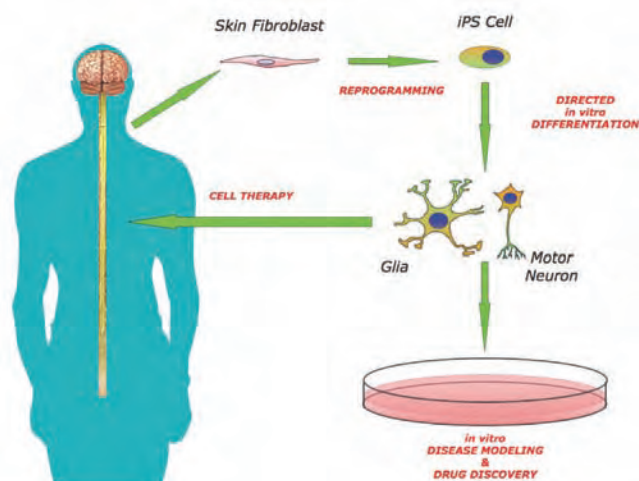


Figure 2: Human iPS technology, together with development of more refined techniques for manipulating the identity of stem cells during their differentiation in vitro, will allow more advanced studies on both the possibility of using such cells for cell replacement and also in improving our understanding of MND at a cellular mechanistic level.

observed is most likely a consequence of stem cells modifying and thus exerting a neuroprotective effect.

This indirect non-cell [MNs] replacement neuroprotective effect of cell transplantation is of growing interest: even if stem cell therapies are not at the moment able to achieve replacement of the lost neurones, the possibility to exploit different mechanisms to slow disease progression might represent a viable therapeutic approach. The precise mechanism of cell mediated neuroprotection is unclear. Implicated mechanisms include cell based secretion of trophic factors and immune modulation. Several studies highlight this beneficial bystander effect: for example, Vercelli and coworkers¹¹ used human bone marrow stromal cells (hMSCs) in a SOD1 model, observing no new MNs after transplantation, but a 35% protection of endogenous MNs. In a different study, Lepore and colleagues¹² demonstrated functional improvement in a similar model following focal transplantation of glial progenitors. In both these studies the actual mechanism of neuroprotection is unknown although some evidence suggests production of trophic factors by transplanted cells may be important. Indirect evidence supporting the importance of neurotrophic factors in a study of transplantation of stem cells engineered to secrete neurotrophic factors is beneficial in a model of MND.¹³

Against this background human studies of stem cell transplantation are increasingly being proposed. Indeed one early clinical phase study is ongoing, studying the effect of foetal neural stem cell transplantation, targeting the cervical spinal cord and using respiratory measures as a secondary outcome, with safety being the primary aim. This study is based at Emory University.¹⁴

Stem cells as a model of MND

Although stem cells for transplantation tend to capture the headlines it is likely that the major benefits of stem cells will actually emerge from in vitro experimental studies that ultimately lead to discovery of new therapeutics. Despite major advances in our understanding of MND, the actual mechanism of MN loss remains unknown. Therefore even in the presence of a successful method to reintegrate functional MNs to regain motor function or modification of the environment to slow progression there is a clear need for further disease models to understand better disease causation.

Notwithstanding the valuable insight from animal models there are several limitations for direct human extrapolation.⁹ These include: inter-species differences ranging from differences in the physiology to species specific gene splicing patterns¹⁵ (particularly important considering for example the prominent role of TDP-43 in splicing regulation¹⁶), disproportionate emphasis on SOD1 based models, and the fact that the techniques used to generate animal models present intrinsic limits to translation. Specifically, the majority of animal models for MND over-express either the wild type or mutant form of the human gene which results in some cases in premature or juvenile rather than age related neurodegeneration. Using human stem cells to model disease can overcome some of these issues. For example generating iPS disease lines from familial patients allows the study of mutant proteins in a physiologically relevant context. There are several examples of successful application of using iPS to model neurological and brain disorders such as spinal muscular atrophy (SMA)¹⁷, inherited Parkinson's disease¹⁸ and schizophrenia.¹⁹

These systems can also be reduced to high throughput assays and as such are a potentially powerful platform for efficient drug discovery. In summary human stem cell biology and its applications offer new approaches to study and potentially treating MND. ♦

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Separating Diagnostic Neurology from Management of Long-Term Neurological Conditions:

A new concept of service delivery



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Imagine admitting a 22-year-old with a stroke. After the initial management, would you prefer to refer him to the local stroke unit or to the neurological rehabilitation unit? Some will prefer the stroke unit where protocols for investigations and assessment are in place. Other clinicians would say that a neurological rehabilitation unit will have more appropriate expertise to meet the needs of a young person with a neurological insult.

The opinions will show the traditional dilemma: should we manage the patient according to his pathology or according to his needs? Many people would feel that the key determinant is the stage of the neurological condition. In the early stage, the focus is on accurate diagnosis, medical stability and interventions that may improve the outcome for scenarios such as thrombolysis for stroke or immunoglobulins for Guillain Barré Syndrome. This necessitates a pathology orientated service provision. The longer the duration of the condition, the more the emphasis shifts to a rehabilitation emphasis with clinical, emotional, social and vocational needs taking centre stage.

This argument begs the question: Is it in the best interest of the patient to have a pathology focused service provision such as Stroke service, Multiple Sclerosis service etc where diagnosis, early interventions and long-term management are combined or is it more appropriate to separate the diagnostic/early intervention service where rapid access, sophisticated investigations and prompt interventions are priorities from long-term management where concepts such as case management, interdisciplinary work and care plans should prevail?

Bolton: Catalysts for change

Royal Bolton Hospital (RBH) is the provider of secondary care for 265,000 Bolton residents. It used to contract consultant neurologists sessions from the regional neuroscience centre based in Salford, 10 miles to the south.

In 2005-2006 the UK government adopted two new strategies to improve the quality and productivity of the health services. These were 'targets-driven service delivery' and adoption of the market forces in health economy using Adam Smith's invisible hand² to improve productivity and efficiency.

RBH struggled to meet the new target of a maximum of 16 weeks waiting for new clinic appointments for neurology patients. They had to postpone or cancel many follow up appointments to meet this target. Unfortunately, this led to huge problems for patients with long-term neurological conditions such as epilepsy, Parkinson's disease (PD) or multiple sclerosis (MS) who needed regular follow ups or occasional prompt consulta-

tions. The community based neurological rehabilitation service found it difficult to access specialist neurology opinion for their patients.

To respond to the government's second drive to encourage health market economy, the regional neuroscience service based in Salford launched a new Centre for Assessment and Treatment (CATS) primarily for Salford patients. This new service integrated the work of the neurologists, neurosurgeons and neuroradiologists enabling them to have a standard patient's journey between GP referral and diagnosis of only few weeks.

The unacceptable delays for neurology follow up appointments galvanised Bolton PCT to rethink the whole ethos of service delivery. After wide consultation with the key stakeholders, Bolton PCT decided to commission the diagnostic neurological services to the Centre for Assessment and Treatment (CATS) based in Salford. Management of long-term neurological conditions moved to a new purpose-built community centre where all the members of the neurological rehabilitation team are based, including the medical team of consultant physicians and specialist nurses (Figure 1).

Implementation

Bolton neurological community team was recognised as the largest in the region, which provided a strong foundation on which to build. Bolton PCT took the opportunity, as it configured the whole service, to address other long standing issues, such as an inappropriate working environment and lack of neuropsychology support. The team moved to a new purpose made building (Figure 2) in 2009. This new physical environment provided adequate office space, excellent gym facilities and modern clinic spaces within the same building. A clinical neuropsychologist was also recruited in the same year.

Negotiations with regional neuroscience to purchase consultant neurology clinic time were successful. The three consultant neurologists doing a minimum of four clinics a week only for patients with long-term conditions, were more than the original neurological input provided in secondary care. Clinical time is also available to the neurologists to meet other members of the team or provide supervision to the specialist nurses. The consultant neurologist clinics were started in 2008.

A part time consultant in rehabilitation medicine has worked with therapists in joint clinics since 2002. These clinics were mainly for patients with complex disabilities or needing single specialist interventions such as chemodenervations. This joint clinic offered the therapists a chance to inform the medical assessment, and the manage-

Figure 1.

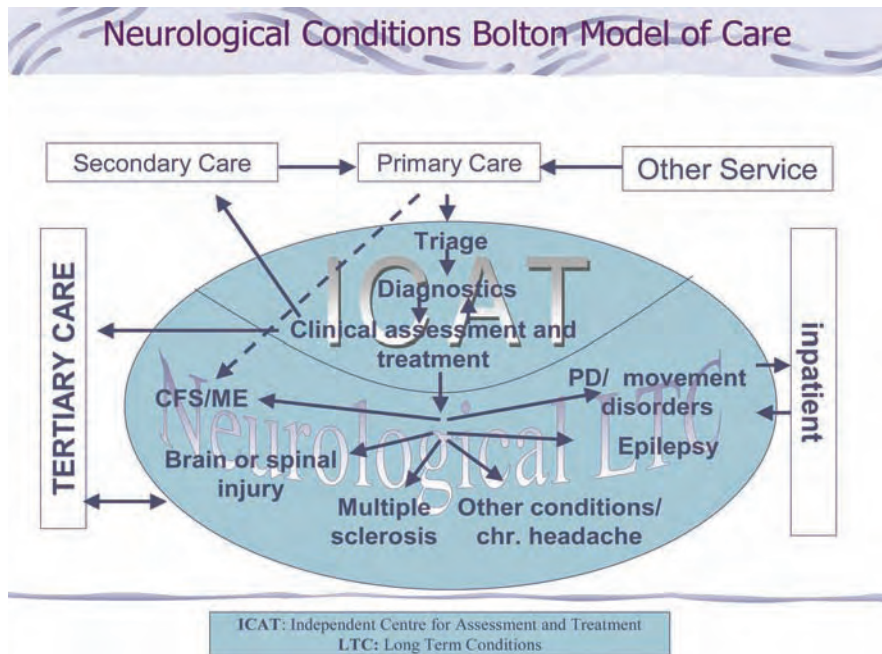


Figure 3.

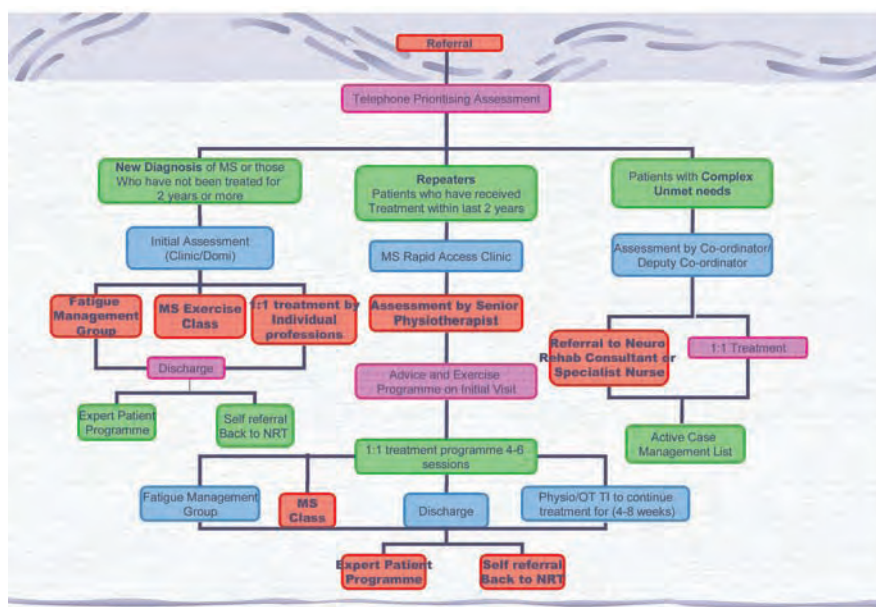


Table 1

Condition	Suitable case manager
Brain injury	OT
MS	MS specialist nurse
Epilepsy	Epilepsy sp. nurse
Parkinson's disease	Parkinson's sp. nurse
CFS/ME	OT
Guillain-Barre Syndrome	Physiotherapist
School leaver's (cerebral palsy)	Physiotherapist / OT

ment plan is usually jointly formulated.

The key component of the service however was based on the concept of case management, which is provided by either specialist nurses for conditions such as MS, epilepsy, and Parkinson's disease, or OTs for brain injury (Table 1).

This team of specialist nurses / case managers is in the forefront of patient care. Their case load is between 600-1000 per nurse. Easy access to specialist consultant advice or therapist opinion is the main factor enabling the case managers to cope with such a high case load. The concept of case managers also saved significant consultants' time as duplication of efforts was kept to a minimum.

The close relationship between the local services and the local patients' support groups was initially instrumental in recognising the scale of the problem. Representatives from the support groups, especially the Neurological Alliance and

Figure 2.



Parkinson's Society, developed Bolton Neuro Voices (BNV) to act as a partner and supervisory body ensuring an effective way to communicate patients' views and experiences to commissioners and providers. BNV canvasses the views of patients and communicate them to the clinical teams during regular joint meetings.

Impact

We believe that our new model of service delivery for patients with long-term neurological conditions is leading to a significant improvement in quality and efficiency. Unfortunately, we will never be able to verify the amount of monetary savings as the traditional model was so chaotic that knowing the amount of money spent in the past was almost impossible.

However, our main objective was and still is to improve the quality of care. Formal audits showed improvements in Did Not Attend (DNA) rates (6.3% in December 2010) and patient satisfaction (100% score service as good or very good). The neurology clinics waiting lists were cut to a maximum of nine weeks.

Our service now complies with most of the quality requirements of the National Service Framework for Long-Term Condition (NSF/LTC) quality requirement 1.³ Concepts such as case management, one point of contact, care plans and patient involvement are integral to our service model.

The service model has also allowed for the development of several care pathways (Figure 3) which facilitated monitoring and audit on one hand and on the other hand minimised duplication and unnecessary referrals.

The future

Following the government advice to separate commissioning from provider arms, NHS Bolton the provider arm of Bolton PCT joined Royal Bolton Hospital Foundation Trust. Our new employer has expressed their commitment to our service and their desire to expand our model to cover the neighbouring districts. ♦

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Mild and Moderate Traumatic Brain Injury in childhood – Who gets admitted?

Traumatic brain injury (TBI) is a major cause of mortality and disability in children and adolescents. The incidence of TBI in children has been estimated at 180-300 per 100 000 children in the UK, of which 5.6 per 100 000 require admission to Paediatric Intensive Care Units and are classified as severe.¹

Mild TBI is the largest proportion of all treated TBI accounting for 80-90% of A&E admissions,² while moderate to severe represent only 10%.³ However, most of the published research to date has concentrated on moderate to severe TBI where long term outcomes are well documented. Established management pathways are in place for moderate to severe TBI according to national guidelines.⁴ It is well known that survivors of moderate to severe head injury can suffer a range of long term outcomes including physical and cognitive deficits, behavioural or emotional difficulties, as well as educational consequences.⁵⁻¹⁰ This has also been documented in mild TBI where not only short term post concussive symptoms are reported,¹¹⁻¹³ but persistent cognitive and behavioural difficulties are encountered in the long term.^{6,7,14,15}

Despite the fact that a large proportion of children sustain mild TBI, and potentially could go on to have long term problems, this group has been relatively neglected nationally in terms of service provision and commissioning. This study was conducted to collect basic epidemiological data on mild or moderate TBI. The objective of the study was to investigate the characteristics and management of mild to moderate TBI among children (aged 0-15 at injury) in the Cambridgeshire area, requiring admission to general paediatric wards. In addition, the study was conducted to increase our knowledge of children with mild/moderate TBI locally.

Methods

The clinical coding team at Addenbrooke's Hospital selected the files with head injury codes (S00, S01, S02, S06, S07, S08 or S09 according to the ICD-10 code), of children under 16 years old living within the Addenbrooke's Hospital catchment area and admitted to the general paediatric wards under the Paediatrics or Neurosurgery teams from January 2005 to December 2009.

Data regarding participants' demographics, previous medical history, details on the incident (date, time, mechanism of injury), pre hospital problems and care, mode of arrival, GCS, problems and investigations in the Accident and Emergency department, length of stay and follow up plans were retrieved retrospectively from the medical records using a proforma. The socioeconomic deprivation was estimated by allocating each postcode to a quintile group according to the Index of Multiple Deprivation 2007. The areas in quintile 5 are least deprived, and those in group 1, most deprived.

Children who lived outside Cambridgeshire and those with orthopaedic or maxillofacial injuries as the main reason of admission rather than the head injury were excluded. Children who went home the same day from the observation unit which is part of the Emergency Department were also excluded as were children whose notes were inaccessible. Overnight stays were included even if the duration of admission was less than 24 hours.

Results

Out of 194 case notes retrieved, 108 were included in the analysis and eighty six files were excluded. The excluded files were children who went home on the same day from the observation unit, children for whom we could not access information and children admitted mainly for orthopaedic care or plastic surgery rather than for neuro-observation.

Characteristics of the study group

The demographic information and characteristics of the group studied are detailed in Table 1.

Index of multiple deprivation

Contrary to our expectations, none of the children in the study lived in the most deprived areas (quintile 1). The majority of children lived in the least deprived areas of which 47 (43.5%) were in quintile 5 and 24 (22.2%) were in quintile 4. Twenty eight children (25.9%) came from areas in quintile 3 and 9 (8.35%) in quintile 2.

Age at time of injury

The age at the time of injury is summarised in Figure 1. There was a significant proportion of infants aged under two years old ($n=44$, 40.7%; mean 9.03 months, range 10 days–22 months). Taken together, children aged under six years accounted for 70% of the sample. In the subgroup of infants, the distribution of age was as follows: 39% for less than six months, 25% between six to 12 months, 27% children aged 13-18 months and 9% were more than 18 months old.

Time of injury

The time of injury was recorded for 96 case notes. Figure 4 highlights the fact that most injuries occurred in mid-afternoon and early evening.

Mechanism of injury by age group

Falls were the most common cause of injury (58%) in all ages and most predominant in the under two year old group (35 out of 63), followed by cycling and pedestrians involved in road traffic accidents in the group of children aged over six years old. Details are shown in Table 2. Most falls happened at home for children below six years old while for older children, this was during recreational activities outside the house.

Table 1: Characteristics of the study group

Variable	Mild/Moderate TBI
Gender: n (%)	
Male	61(56.4)
Female	47(43.3)
GCS: n (%)	
14-15(Mild)	74(97.3)
9-13(Moderate)	2(2.6)
Not available	32
Pre-hospital problems: n (%)	
Vomiting	55(50.9)
LOC	16(14.8)
Amnesia	6(5.5)
Fit	3(2.3)
Post concussive symptoms	18(16.1)
No symptoms	22(20.3)
Mode of arrival: n (%)	
Self referral	57(57)
Ambulance	31(31)
GP referral	12(12)
Not available	8
Admitting team: n (%)	
Neurosurgery	73(67.5)
Paediatrics	31(28.7)
A&E	3(2.7)
General surgery	1(0.9)
Length of stay: n (%)	
<24 hours	21(19)
24 hours	70(64.8)
2 nights	11(10.1)
3 nights	2(1.8)
5 nights	3(2.7)
21 nights	1(0.9)

Investigations

CT scan of the head was performed in 48 participants (44.4%) and not requested for the remaining 60 (55.5%). Among children who were not scanned, the largest proportion were toddlers (27), followed by the over six year old age group (18) and 15 children aged two to five years old. The scan findings were normal in the majority of cases (30, 62.5%). The abnormalities found in 18 CT scans were as follows: eight (44.4%) cases of isolated skull fracture, four cases of fracture associated with haemorrhage (22%) and with haematoma for two children (11.1%). One case was found in each of the following abnormalities: parenchymal bleed, contusion with haematoma, fracture of zygoma, fracture of antrum and nasal bone. Skull X-ray was requested for six children and revealed skull fracture in four cases, and a suspicion of left coronoid fracture in one case. It was reported as normal in one participant.

Follow-up plans

Thirty three children had a follow-up appointment after discharge; this represented 30.6%. Of these 33 children, 23 had CT scan and 16 of them were reported as abnormal. No follow-up plans were recorded in 75 files (69.4%). Head injury advice sheets were handed to 36 families and the health visitor was notified for three children. Verbal head injury advice was documented in four cases. No advice was documented in 31 files.

Discussion

The majority of children admitted for neuro-observation following a mild or moderate TBI were under six years old with a predominance for under two year old group (44 / 71). Adolescents were less represented on the wards despite the number of attendances in the Accident and

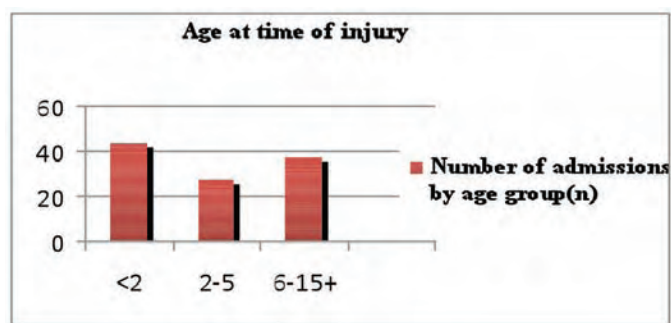


Figure 1: Age at time of injury.

Table 2: Mechanism of injury by age group

Injury mechanism	Age group			
	<2	2-5	6-15	Total (%)
Fall	35	21	7	63(58)
Cyclist		3	7	10(9.2)
RTA pedestrian			6	6(5.5)
RTA passenger			2	2(1.8)
RTA cyclist			1	1(0.9)
Sport			3	3(2.7)
Alcohol related			4	4(3.7)
Unknown	4			4(3.7)
NAI	1			1(0.9)
Others	4	3	6	13(12)
Total	44	27	37	108

Emergency Department (A&E). The small number of adolescents admitted to general paediatric wards probably reflects the use of CT scan and discharge home from A&E for older children, while younger ones were more likely to have been kept for observation as inpatients. The high proportion of admissions of young children in this study can be partly explained by the timing of the incident. Most injuries occur in the early evening and children are therefore brought to A&E late in the working day. Most clinicians, particularly trainees will take a cautious approach with a head-injured young child and will admit for observation with or without a CT scan. This decision is further justified by the National Institute of Clinical Excellence guidelines which recommend observation of patients with unresolved neurological signs or continuing worrying signs of concern to the clinician. The implication of this is that increased scanning hours or an increased presence of senior medical staff during the evening might further reduce the need for admissions. We have found that in 63% of cases, the reported cause of injury was a fall. This is consistent with the findings of Ventsel who reported 63.6%.¹⁶ These findings are also consistent with previous epidemiology studies^{17,18} indicating the prevalence of falls in younger children.

The results of the index of multiple deprivation in this study, reflects the general socioeconomic status of the population in Cambridgeshire. Based on the annual report (2009) from the Association of Public Health Observatories (APHO), the proportion of residents who live in the most deprived areas is low in Cambridgeshire. In the national study on admissions to hospital following head injury, Alan Tenant also found that Cambridgeshire was included in the cluster of rural areas with a low level of deprivation, indicating less deprived areas.¹⁹

CT head scan was not requested in 60 (55.5%) cases. Of these 60 children, 27 were aged under two years. It is clear that the infants were most likely to be admitted without a CT of head requested. NICE guidelines emphasise the early diagnosis of clinically important brain and cervical spine injuries, using a sensitive and specific clinical decision rule with early imaging. Admission to hospital is linked to imaging results, on the

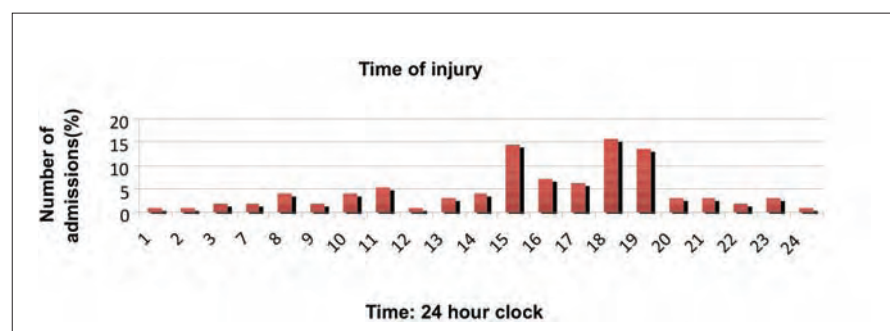
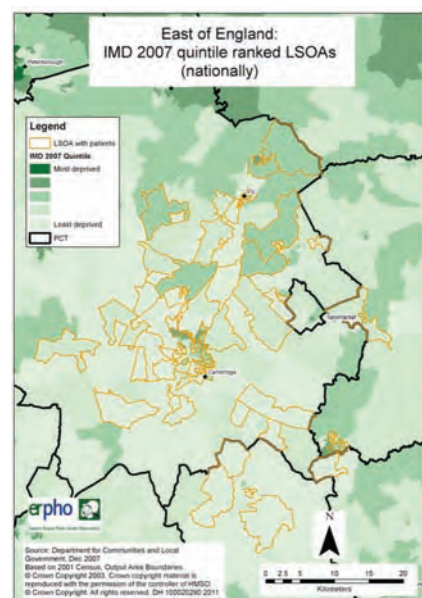


Figure 2: Time of injury.



The map shows the areas (Lower Super Output Areas) with patients and the arrangement of these areas in rank order according to the deprivation scores in the Index of Multiple Deprivation 2007.

basis that patients who do not require imaging are safe for discharge (given that no other reasons exist for admission) and those who do require imaging can be discharged after negative results (given that no other reasons exist for admission). However, some studies have argued that the radiation dose from a CT scan, particularly in a young child, is significant and may be associated with adverse effects such as increased risk of brain and thyroid tumours,²¹ and possible effects on intellectual development in adulthood.²² An awareness of the potential risks related to radiation levels in CT neuroimaging may be partly responsible for the decision by clinicians to admit toddlers for observation rather than perform a scan. In line with the radiation exposure management, the guidelines highlight that every effort should be made to minimise radiation during imaging of the head and cervical spine, while ensuring that image quality and coverage is sufficient to achieve an adequate diagnostic study.

This study has found that the follow-up rate after mild TBI was low at 30.6%. Hawley found in North Staffordshire Hospital, a rate of 30% for all injuries together (mild, moderate and severe) and 21.7% specifically in the mild group.⁶ This very low follow-up rate is a cause for concern in this group, particularly given

what we know about the potential adverse effects of head injury in childhood. It was also raised as a cause for concern in a study of parents' perspectives one to five years after injury.²⁰ The majority of children who were followed up had a CT scan and in almost half of cases (16 out of 33) the findings were abnormal. This probably represents a more significantly affected subgroup of children.

NICE guidelines recommend that school nurses should be notified of the admission for all school-aged children who received head or cervical spine imaging. We noted that this detail was not found in the records. Communication between hospital and school personnel is essential. Following mild traumatic brain injury, some children may present with memory problems, attention/ concentration problems, difficulties with school work, as well as challenging behaviour.⁷ Providing schools with information about traumatic brain injury and possible long-term impairments is important, so that children receive appropriate support.

Conclusions

The study has gathered descriptive data on a group of mild or moderate head injury admissions to Addenbrooke's Hospital, Cambridge, UK over a five year period. The findings to highlight are:

Firstly, toddlers (infants) who experienced falls represented a large proportion of the group. Secondly, the CT scan of head was not performed in more than half cases. Finally, routine follow-up is almost nonexistent after mild TBI, apart from children whose CT scans reveal abnormalities. This is a challenge and could be resolved by developing integrated and responsive care pathways to meet the needs of this group of children. The need for follow-up and responsive services is imperative to ensure that any potential difficulties can be picked up early and consequent interventions applied. Not all of these children will need follow-up, but we need to identify and call back those with problems. The question of how best to identify the subset of children who need follow-up and the proportion of those who may present problems after mild TBI needs to be answered. A study on outcomes following mild TBI in children aged less than six years at the time of injury is needed to identify the proportion of children who develop problems after mild TBI and the nature of these difficulties. ♦

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Leber Hereditary Optic Neuropathy – Therapeutic Challenges and Early Promise

Leber hereditary optic neuropathy (LHON) is the most common primary mitochondrial DNA (mtDNA) disorder in the United Kingdom, with a minimum prevalence of 1 in 31,000.^{1,2} Three mtDNA point mutations account for ~90% of all LHON cases and m.11778G>A is the most frequently identified (~70%) pathogenic variant worldwide (Table 1).^{3,4} It is an important cause of severe visual loss among young adults with a peak age of onset in the second and third decades of life. Management is mostly supportive but recent developments in LHON research are pointing the way towards more effective treatments for this blinding mitochondrial disorder.

Clinical features of LHON

LHON classically presents with acute or subacute painless loss of central vision. The initial visual loss is severe with most patients achieving best corrected visual acuities of 6/60 or worse.^{3,4} There is an associated dense central scotoma and a marked reduction in colour perception. Despite this global reduction in optic nerve function, the pupillary light reflexes are relatively preserved,

and this distinctive feature has been ascribed to a special class of melanopsin-containing retinal ganglion cells (RGCs), which are less vulnerable to the downstream consequences of the mtDNA LHON mutations.⁵ Bilateral optic nerve involvement occurs in ~25% of LHON cases. If sequential, the second eye is invariably affected within one year of disease onset, unilateral optic neuropathy being exceptionally rare in LHON.^{3,4}

In the acute phase, optic disc hyperaemia, peripapillary telangiectatic vessels, vascular tortuosity, and retinal nerve fibre layer oedema can be observed, the latter being due to RGC axonal stasis (Figure 1).^{3,4} In the pre-molecular era, these fundal abnormalities were particularly informative, allowing a presumptive diagnosis of LHON to be made, especially when supported by a maternal family history of early-onset visual loss. In 20-40% of acute cases, the optic discs look entirely normal and these patients are often incorrectly labelled as having functional visual loss.^{3,4} Pallor of the neuroretinal rim develops within six weeks of disease onset and it is initially more apparent temporally due to the accelerated loss of RGC

Table 1: Mitochondrial DNA variants associated with LHON

	Mitochondrial Gene	Nucleotide Change
Common variants (~ 90%)	MTND1	m.3460G>A*
	MTND4	m.11778G>A*
	MTND6	m.14484T>C*
Rare variants (~ 10%)	MTND1	m.3376G>A, m.3635G>A*, m.3697G>A, m.3700G>A, m.3733G>A*, m.4025C>T, m.4160T>C, m.4171C>A*
	MTND2	m.4640C>A, m.5244G>A
	MTND3	m.10237T>C
	MTND4	m.11696G>A, m.11253T>C
	MTND4L	m.10663T>C*
	MTND5	m.12811T>C, m.12848C>T, m.13637A>G, m.13730G>A
	MTND6	m.14325T>C, m.14568C>T, m.14459G>A*, m.14729G>A, m.14482C>A*, m.14482C>G*, m.14495A>G*, m.14498C>T, m.14568C>T*, m.14596A>T
	MTATP6	m.9101T>C
	MTCO3	m.9804G>A
	MTCYB	m.14831G>A

* These mtDNA variants are definitely pathogenic. They have been identified in ≥ 2 independent LHON pedigrees, showing segregation with affected disease status. The remaining putative LHON mutations have been found in singleton cases or in a single family, and additional evidence is required before pathogenicity can be irrefutably ascribed.^{3,4}

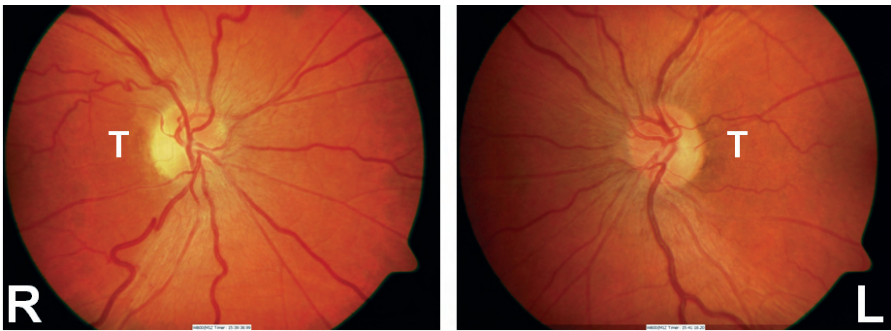


Figure 1: Fundal appearance in acute and chronic LHON stages.
This 47-year-old m.11778G>A male carrier experienced visual loss in his right eye first, followed by his left eye eight months later. These fundal pictures were taken one month after the left eye had become involved. Best corrected visual acuities at that point were counting fingers in the right eye and 6/36 in the left eye. There is vascular tortuosity in both eyes and temporal pallor of the right optic disc (chronic stage) due to the earlier and more pronounced loss of RGC axons within the papillomacular bundle, which sub-serves the central 10° of the visual field. There is mild hyperaemia of the left optic disc, in keeping with the recent onset of visual symptoms in that eye (acute stage).
(L = left eye; R = right eye; T = temporal quadrant corresponding to the papillomacular bundle)

Table 2: Risk of visual loss for relatives of LHON probands		
	Risk of visual loss	
	m.11778G>A	m.14484T>C
Siblings		
Brother	25%	28%
Sister	8%	5%
Sister's children		
Nephew	41%	30%
Niece	7%	3%
Maternal first cousins		
Male	30%	19%
Female	7%	4%
The recurrence risks for the m.3460G>A mutation have not been determined in a large number of pedigrees. However, these are unlikely to differ significantly from the reported estimates for the m.11778G>A and m.14484T>C LHON mutations. ^{3,4}		

axons within the papillomacular bundle. Extra-ocular features such as cardiac conduction defects, peripheral neuropathy, dystonia, and myopathy are thought to be more common among LHON carriers compared with the general population.^{3,4} There is also a well-established association between the three primary LHON mutations and a demyelinating illness, which interestingly is clinically and radiologically indistinguishable from multiple sclerosis (Harding's disease).⁶ Other rarer pathogenic mtDNA variants have been linked with more atypical 'LHON plus' syndromes where the optic neuropathy is complicated by prominent spastic dystonia, ataxia, juvenile-onset encephalopathy, and psychiatric disturbances.^{3,4}

Visual prognosis

The visual prognosis in LHON is poor and most patients remain legally blind. The likelihood of visual recovery is greatest with the m.14484T>C mutation, least with the m.11778G>A mutation, and intermediate with the m.3460G>A mutation.^{3,4} Although delayed visual recovery has been reported, maximal improvement in visual function usually occurs within the first year, if it occurs at all. The appearance of small islands of vision within the patient's visual field (fenestrations) can

greatly help scanning vision, especially if the central scotoma becomes concurrently less dense.

Genetic counselling

The mitochondrial genome is maternally inherited and thousands of mtDNA molecules are present in metabolically-active cells. As a result of this high-copy number genome, two possible situations can arise, known as homoplasmy and heteroplasmy. Among LHON families, 85-90% of carriers are homoplasmic for the mtDNA mutation, i.e. 100% mutant, whereas the remainder are heteroplasmic harbouring a mixture of both wild-type and mutant mtDNA species.² The risk of disease conversion is low if the mutational load is below the threshold level of 60%.⁷ Male LHON carriers can be reassured that their children will not inherit their mitochondrial genetic defect. On the other hand, female LHON carriers will transmit the mutation to all their offspring. For the minority of mothers with heteroplasmic LHON mutations, it is difficult to accurately predict the mutational level that will be transmitted since rapid generational shifts in mitochondrial allele frequencies can occur due to the 'mitochondrial bottleneck' operating in the female germline.⁸ Based on published figures, some indication of recurrence risks can

be provided to maternal relatives of a LHON proband (Table 2).

Although it is not possible to predict whether or when a LHON carrier will be affected, epidemiological studies have identified major risk factors for visual loss, namely age, sex and environmental exposure.^{2,4} Over 90% of LHON carriers who will experience visual failure will do so before the age of 50 years. In addition, LHON is characterised by a marked sex bias, male carriers having a ~50% lifetime risk of developing the optic neuropathy compared with only ~10% for female carriers. Unaffected LHON carriers should be strongly advised not to smoke and to minimise their alcohol intake, not only as a general health measure, but because smoking, and to a lesser extent excessive alcohol intake, have been associated with increased risks of disease conversion.^{3,4} In one large study comparing 196 affected and 206 unaffected carriers from 125 LHON families, light and heavy smokers were twice and three times more likely to lose vision compared to non-smokers, respectively.⁹

Treatment strategies

Mitochondria provide the bulk of the cell's adenosine triphosphate (ATP) requirements through the tightly-regulated control of electron flux along the mitochondrial respiratory chain. All three primary LHON mutations; m.3460G>A, m.11778G>A, and m.14484T>C disrupt key polypeptide subunits of complex I, resulting in a significant bioenergetic deficit and raised levels of reactive oxygen species (ROS).¹⁰ An intriguing aspect of the pathophysiology of LHON still remains: why are RGCs selectively vulnerable to disturbed mitochondrial function? Several hypotheses have been proposed based on the distinct anatomical, physiological, and cytoskeletal arrangements present within the optic nerve.¹⁰ Notwithstanding these unresolved issues, the final pathological outcome in LHON is apoptotic RGC loss and the aims of treatment for this disorder are threefold: (i) to prevent initial visual loss among LHON carriers, (ii) to protect the unaffected fellow eye in patients with unilateral optic neuropathy, and (iii) to preserve visual function in already compromised optic nerves.

Neuroprotection

Various treatment 'cocktails' have been used to mitigate the deleterious impact of mitochondrial dysfunction on RGC survival.^{3,4} Coenzyme Q10 (CoQ10) is a quinone analogue and based on limited evidence, it is frequently prescribed to patients with mitochondrial disease. Idebenone is a related compound, a shorter-chain synthetic benzoquinone analogue, which is thought to have a better bioavailability profile compared with CoQ10.¹¹ Idebenone is able to bypass complex I inhibition and by shuttling electrons directly from the cytosol to complex III, ATP production is optimised with a decrease in toxic ROS levels.¹¹ This dual mode of action is an attractive therapeutic combination and anecdotally, some patients with LHON have experienced

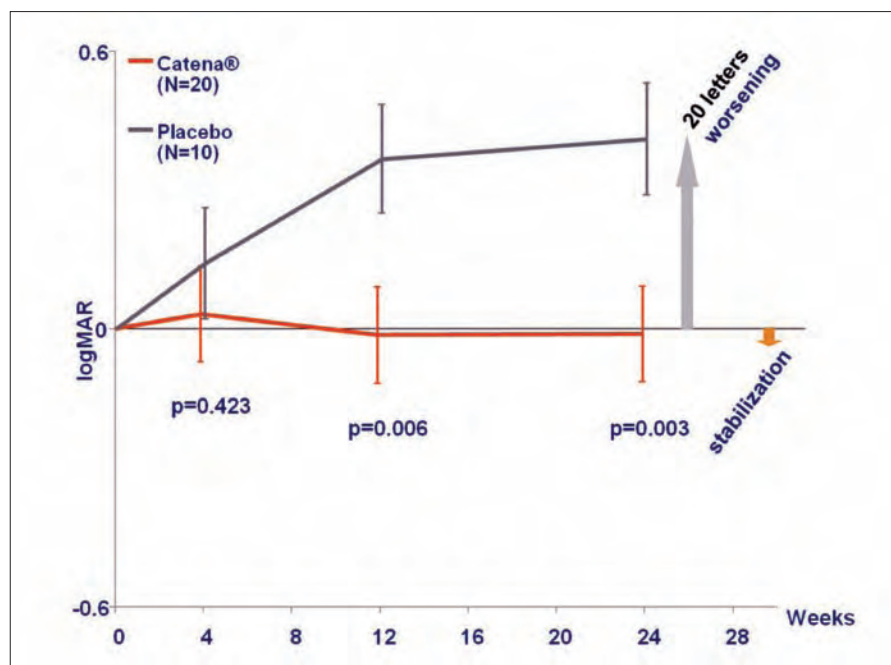


Figure 2: Change in best visual acuity for patients with discordant visual acuities at baseline. Catena® is the formulation of idebenone provided by Santhera Pharmaceuticals (Liestal, Switzerland). Patients randomised to the treatment arm received a total dose of idebenone of 900mg per day, with 300mg taken three times a day during meals. Of the 85 patients enrolled into the RHODOS trial, 30 had discordant visual acuities at baseline, which was defined as a difference of more than 0.2 LogMAR between the two affected eyes.¹² This degree of visual disparity is rare in late-stage chronic LHON where patients usually have fairly symmetrical visual loss between the two affected eyes. Patients with discordant visual acuities at baseline were therefore at highest risk of further deterioration in the least affected eye, accounting for the greater treatment effect observed in this particular subgroup. (LogMAR = logarithm of the minimum angle of resolution)

significant visual recovery following treatment with idebenone.^{3,4} In collaboration with clinical partners in the UK, Germany and Canada, we therefore conducted a multicentre double-blind randomised controlled trial (RCT) to investigate the safety, tolerability, and efficacy of high-dose idebenone in LHON. RHODOS (Rescue of Hereditary Optic Disease Outpatient Study) successfully enrolled 85 patients harbouring the three most common mtDNA LHON mutations: m.3460G>A (n=11), m.11778G>A (n=57), and m.14484T>C (n=17).¹² These patients were randomised in a 2:1 ratio to receive either high-dose idebenone (900mg) or placebo over a 24-week treatment period. A major finding of the RHODOS trial is that patients with LHON were more likely to benefit from idebenone if they were treated relatively early in the course of the disease (Figure 2). No adverse drug reactions were reported and idebenone is currently under review by the European Medicines Agency for regulatory approval. Besides idebenone, other neuroprotective agents are also being investigated as potential treatment options in LHON. In an open-label study of four patients with acute LHON treated within 90 days of disease conversion, the antioxidant α -tocotrienol-quinone (EPI-743), a vitamin E derivative, has shown early promise and a RCT is underway to study this compound further (http://www.aosonline.org/annualmeeting/am_program.pdf, Accessed 8th of August 2011). Although their usefulness has yet to be established clinically, a marked amelioration in mitochondrial oxidative function was observed in

cellular LHON models following supplementation with oestrogen-based compounds.¹³

Gene therapy

Gene therapy for primary mtDNA disorders is challenging. The mitochondrial inner membrane is relatively impermeable and a highly-efficient vector is needed to transfect a sufficient number of mitochondria per cell in order to rescue the disease phenotype. To circumvent these technical difficulties, a possible solution is the so-called allotopic approach where the gene of interest is transfected into the nuclear genome, and the encoded protein is engineered with a specific targeting sequence that facilitates its uptake into the mitochondrial compartment.¹⁰ RGC loss was dramatically reduced, in both in vitro and in vivo experimental LHON models, by transfecting them with an adenovirus vector containing the human SOD2 gene.¹⁴ In these conditions of heightened oxidative stress, the over-expression of the antioxidant enzyme superoxide dismutase is thought to promote RGC survival by exerting an anti-apoptotic influence. Another attractive and more direct approach is to replace the dysfunctional subunit encoded by the mtDNA LHON mutation. Proof of this concept has recently been demonstrated in a rat model harbouring a defective ND4 gene with the m.11778A>G mutation.¹⁵ Visual loss was reversed by transfecting RGCs with the wild-type version of the ND4 gene, the level of transgene expression being sufficient to rescue RGCs and maintain normal physiological responses.

Looking into the future

RHODOS is the first RCT for a primary mitochondrial disorder and the results obtained with high-dose idebenone are encouraging. A number of novel neuroprotective agents are currently in the pipeline for other mitochondrial cytopathies and these could also prove beneficial for patients with LHON. Gene therapy is a valid complementary approach to pharmacological intervention but long-term safety data is essential before human clinical trials can be advocated. After two decades of sustained research, we are now at the start of an exciting translational phase not only for LHON, but for other mitochondrially-determined optic neuropathies, which as a group represent an important cause of chronic visual morbidity in the population. ♦

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Defining the Mitochondrial POLG-Related Spinocerebellar Ataxia and Epilepsy in Norway



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Mitochondria are the major producers of cellular energy and failure of this process is associated with a range of devastating diseases that affect both children and adults. In addition to causing disease, mitochondrial dysfunction is also implicated in basic cellular processes such as apoptosis, the ageing process and the development of cancer. In addition to their essential role in energy metabolism, mitochondria have their own DNA (mtDNA), a small, maternally inherited genome that encodes 13 subunits of the respiratory chain. The remaining respiratory chain subunits and all other mitochondrial proteins, including those involved with mtDNA replication and homeostasis, are encoded by nuclear genes.

DNA-polymerase γ (pol γ) is the enzyme that replicates and repairs mitochondrial DNA (mtDNA). The enzyme comprises one catalytic subunit (pol γA), and two accessory subunits (pol γB). Pol γA consists of a polymerase (replicating) domain and an exonuclease (proof-reading) domain, separated by a large linker region to which the accessory subunits bind.¹ These proteins are encoded by genes found on the chromosomes. Initially, mutations in the Pol γA gene were identified in families with autosomally inherited, progressive external ophthalmoplegia (PEO).¹ Subsequently, more than 130 pathogenic mutations in Pol γA have been described causing a wide spectrum of neurological syndromes ranging from adult onset PEO / myopathy to severe infantile encephalopathies including Alper's syndrome, parkinsonism and the syndrome of mitochondrial spinocerebellar ataxia and epilepsy (MSCAE), also known as mitochondrial recessive ataxic syndrome (MIRAS),^{1,2} that is the focus of this article.

As with all competitive science, our studies were performed on a backdrop of intense activity focussed around nuclear genes causing mitochondrial disease, particularly polymerase gamma. Our work on MSCAE started in 2003 while studying several patients with the phenotype of progressive ataxia, PEO and epilepsy, a combination that strongly suggested a mitochondrial aetiology. Initially, however, while skeletal muscle histochemistry showed scattered COX deficient fibres in

some, both biochemical studies and standard genetic studies of mtDNA failed to uncover a defect; respiratory chain activities were normal and both sequencing and Southern blotting of mtDNA showed no evidence of mutation. Help solving this puzzle was provided by colleagues in Newcastle, UK, who were at that time developing a real-time technique for detecting mtDNA rearrangements. With their help, we were able to show that our patients had multiple mtDNA deletions in their muscle. With this confirmation of mitochondrial involvement, we refocused our efforts on elucidating the genetic cause and chose Pol γA as the first candidate. This work, which was also a collaboration with colleagues from Milan, Italy, identified two Pol γA mutations, c.1399G>A (p.A467T) and 2243G>C (p.W748S), in all patients.² Further, we established that these mutations were present at high levels in the population of Western Norway with frequencies of 1:100 for each.

Despite the intense focus surrounding polymerase gamma at this time, including the finding that it was responsible for different diseases, including Alper's, parkinsonism and complex forms of ataxia, we were still surprised when we began identifying large numbers of patients with the same two mutations identified in our first study. Patients with ataxia and aggressive epilepsy were referred to us from colleagues both in neurology and paediatrics. In a relatively short time, we collected 26 patients from 20 families all carrying the c.1399G>A or/and c.2243G>C Pol γA mutations, either in the homozygous state or in combination. With such a large material we were able to make a full description of the clinical spectrum and natural history of the syndrome and correlate clinical features with the genotype.³ This study led us to the discovery that genotype had a major impact on survival; patients who were homozygous for one or other of the mutations had significantly better survival than those who were compound heterozygous in trans (1399G>A/2243G>C). As yet, we are unable to explain the poorer prognosis seen in compound heterozygotes, but have confirmed that the result also holds true when including all patients reported with these two mutations. Our analysis

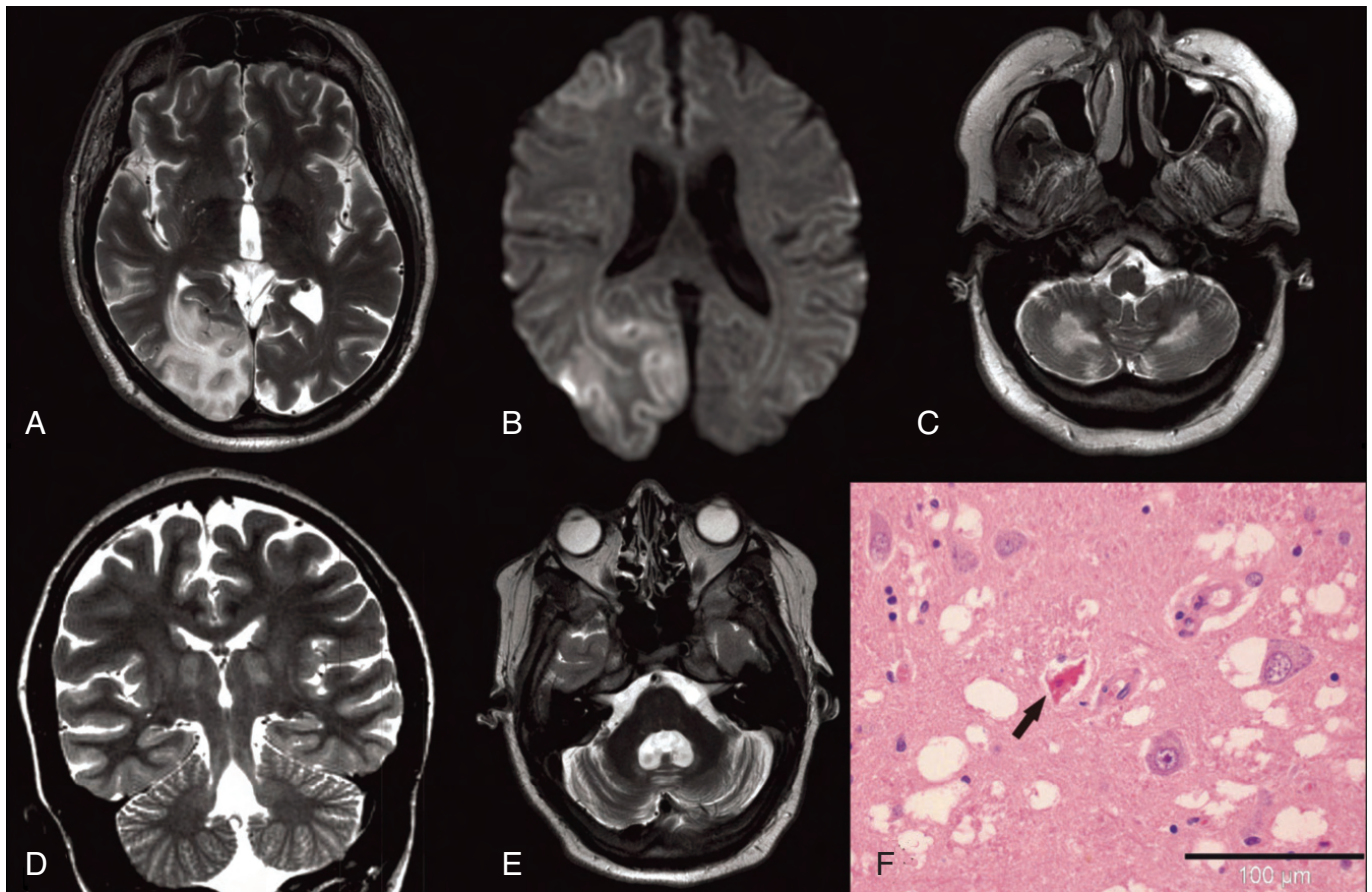


Figure. Representative cerebral MRI and histopathological findings in MSCAE. A. axial T2 weighted MRI showing a large right occipital stroke-like lesion. B. Diffusion weighted image ($b=1000$) of the same lesion showing restricted water diffusion in the cortex (confirmed by ADC measurements). C. axial image showing high T2 signal intensity in the cere-

bellar white matter. D. coronal MRI showing high T2 signal lesions of the thalami. E. axial T2 weighted image depicting atrophy of the cerebellum and dentate nuclei and high T2 signal in the latter. F. hematoxylin and eosin staining of the thalamus with a single necrotic eosinophilic neuron surrounded by normal looking neighbouring cells.

also showed that sodium valproate was highly toxic in this group of patients, leading to fatal hepatic necrosis in several; we suspect, moreover, that the long established link between mitochondrial disease and this anticonvulsant is indeed entirely due to its' specific toxicity for these patients.

Since other groups were also reporting significant numbers of patients with Pol γ A mutations and ataxia, we were able to compare their clinical findings with ours. One interesting difference, particularly between patients from Finland and our cohort, was the frequency and destructiveness of the epilepsy occurring in Norwegian patients. Together with our colleague, Bernt Engelsen, we analysed the type and course of the epilepsy and found that our patients developed a specific syndromic epilepsy with a predilection for the occipital lobes. Irrespective of genotype, our patients developed an epileptic syndrome showing initial features of occipital lobe epilepsy.⁴ Subsequently, the epilepsy becomes generalised and patients experience simple and complex partial seizures, myoclonus and both epilepsia partialis continua and frequent convulsive status epilepticus. Prognosis was extremely poor for those who developed convulsive status epilepticus and despite heroic treatment, most died and those surviving were usually severely damaged.⁴

The latest phase of our work has focussed on describing the neuroradiological features of the syndrome and elucidating the cellular mechanisms underlying neuronal dysfunction and death. Using a combination of MRI and histopathological investigation we have explored what is happening at the cellular level, focussing particularly on the central nervous system since this is the major site of disease in MSCAE.⁵ Our MRI studies identified a specific pattern of brain involvement; findings could be classified into three groups, progressive cerebral and cerebellar atrophy, chronic focal signal changes affecting the thalamus, cerebellar white matter and medulla oblongata, and hyperacute, rapidly evolving stroke-like cortical lesions. The latter occurred during acute episodes of decompensation with rapidly progressive encephalopathy and convulsive status epilepticus. By studying MRI taken very early in lesion evolution, we found that stroke-like lesions in MSCAE showed restricted water diffusion suggesting intracellular water sequestration i.e. cytotoxic cerebral oedema. As we did not find evidence of cerebral ischaemia, the cytotoxic oedema was attributed to primary neuronal energy failure caused by respiratory chain dysfunction due to mtDNA damage (Figure 1A-E).

The occurrence of energy deficiency in neurons was further supported by histopatho-

logical findings including selective neuronal loss and eosinophilic necrosis (Figure 1F) in the cerebral cortex and thalamus, and cortical laminar necrosis.⁵

Our studies have confirmed Pol γ A as a major cause of syndromic mitochondrial disease in adults. We have defined the phenotype and, in particular, the occipital epilepsy and shown that genotype is an important prognostic factor. Lastly, we have confirmed that the hitherto assumed role of energy failure in disease evolution. In the future we hope to elaborate further the cellular consequences of Pol γ A mutation in both cellular and animal models in order to identify possible treatments. ♦

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Intraventricular Haemorrhage of the Newborn



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Intraventricular haemorrhage occurs frequently in premature neonates. Large haemorrhages cause post-haemorrhagic ventricular dilatation, often requiring permanent CSF diversion. Elevated intracranial pressure, inflammatory cytokines and peri-ventricular white matter distortion cause significant and permanent neurological disability. Progressive ventricular expansion is best controlled initially by regular aspiration through a ventricular access device. A combination of drainage, fibrinolysis and irrigation with artificial CSF, also known as DRIFT, has been shown to improve neuro-developmental outcome at two years in a randomised study. It does not, however, reduce the need for ventriculoperitoneal shunt insertion. Future advances are likely to involve close collaboration between neonatologists and neurosurgeons.

Introduction

Intraventricular haemorrhage (IVH) remains an important problem in neonatal care and is characteristic of the premature infant. Improvements in neonatal care have led to a persistent decline in the mortality associated with prematurity. Currently, up to 90% of infants with birth weights between 500 and 1500g survive the neonatal period.¹ Although advances in neonatal care have reduced the incidence of IVH in premature neonates, overall rates of IVH have generally been in the 20 to 25% range over the last two decades.² IVH is more common at lower birth weights, and for infants weighing between 500 and 750g incidence is up to 45%.¹ Post-haemorrhagic ventricular dilatation (PHVD) occurs in over half of those neonates with large bleeds.³ Up to 60% of these neonates become dependent on cerebrospinal fluid (CSF) shunts.⁴ Neurological outcome ultimately depends not only on the extent of periventricular leucomalacia related to injury to the oligodendrocyte precursors secondary to prematurity, but also on the management of PHVD and the complications related to CSF diversion, such as shunt malfunction and infection.^{5,7}

Pathophysiology

In prematurity, the source of the haemorrhage is the germinal matrix, located in the subependymal

region. The germinal matrix gives origin to the cerebral neuroblasts and glia; it is highly cellular and gelatinous and is richly vascularised by capillaries that are poorly supported by muscle or collagen.⁸ It involutes in a rostro-caudal direction over the final 12 to 16 weeks of gestation.⁹ It is a fragile structure, and is prone to haemorrhage following abrupt changes in cerebral blood flow. In the premature neonate, such changes are often related to perinatal asphyxia and respiratory distress syndrome.¹⁰ IVH at term is rare and may be associated with trauma, vascular malformation or coagulopathy.

The occurrence of PHVD is directly related to the quantity of intraventricular blood. It may occur early as a result of aqueductal obstruction by haematoma, but more commonly it occurs as a result of a progressive obliterative arachnoiditis, involving the basal cisterns and the outlet foramina of the fourth ventricle.¹¹ This disturbs the flow of CSF from the ventricles, where most is produced, to its absorption sites in the subarachnoid space, leading to a combination of communicating and obstructive hydrocephalus.

A number of cytokines, particularly transforming growth factor (TGF) β , have been associated with this process. TGF- β is a potent fibroblast activator, and upregulates genes expressing extracellular matrix proteins; these proteins are central to the development of obliterative arachnoiditis.¹² TGF- β is not only secreted by astrocytes, meningeal cells and choroid plexus epithelial cells in response to inflammation, but is also released from alpha granules in the platelets within the IVH.¹³ In a clinical study, total TGF- β levels were higher in infants who developed PHVD, and were higher still in those who required insertion of a ventriculoperitoneal shunt.¹⁴ A rat pup model of PHVD has demonstrated increased TGF- β , laminin and fibronectin in the ependyma and subependymal tissue.¹⁵ However, intraventricular administration of decorin and oral administration of pirfenidone, both TGF- β antagonists, in the same rat pup model, did not lead to a reduction in ventricular size.^{16,17} Other cytokines, such as vascular endothelial growth factor (VEGF), are also likely to be involved.¹⁸

Neurological outcome ultimately depends not only on the extent of periventricular leucomalacia related to injury to the oligodendrocyte precursors secondary to prematurity, but also on the management of PHVD and the complications related to CSF diversion, such as shunt malfunction and infection

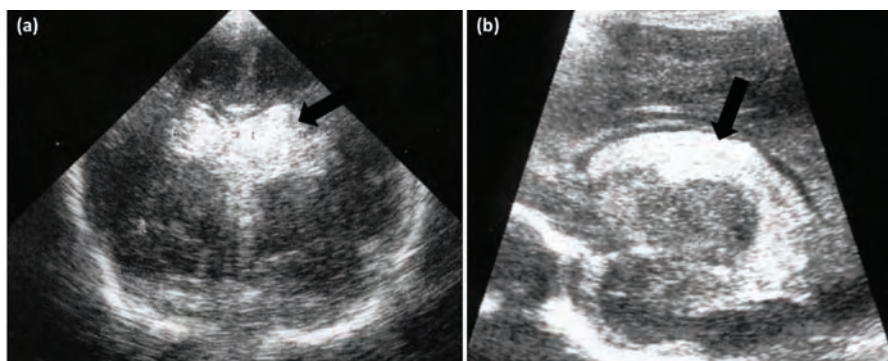


Figure 1: Coronal (a) and sagittal (b) ultrasound scans demonstrating hyperechoic intraventricular haemorrhage (black arrows).

The IVH itself is neurotoxic. Iron released from haem days after haemorrhage catalyses lipid peroxidation and exacerbates excitotoxicity.¹⁹ Non-protein bound iron levels in the CSF are markedly increased for several weeks after human neonatal IVH, enhancing the formation of reactive oxygen species at a time when antioxidant enzymes are not yet fully developed.²⁰ In addition, the coagulation cascade releases thrombin, known to induce apoptosis in cultured neurons and astrocytes.²¹

The progressive accumulation of CSF in PHVD causes pressure on the peri-ventricular white matter, expanding the ventricles, and to a lesser extent, the compliant unfused skull, at the expense of brain volume. Neonatal intracranial pressure is normally under 6mmHg, but in the context of untreated PHVD it may rise to 10 to 15mmHg.²² It is the combination of inflammation, distortion, pressure and free radicals that causes significant injury to the poorly perfused neonatal white matter.

Diagnosis and classification

Both IVH and PHVD can be readily diagnosed on cranial ultrasonography (Figure 1). The degree of IVH is traditionally defined according to the Papile classification.²³ This recognises four kinds of IVH from mild to severe, as follows: grade I – subependymal haemorrhage; grade II – IVH; grade III – IVH with ventricular dilatation; grade IV – IVH with ventricular dilatation and parenchymal extension. Intraparenchymal involvement, however, is now no longer thought to represent merely an extension of the haemorrhage, but rather a venous haemorrhagic infarction, related to obstruction of the terminal vein at the ventricular angle by a large IVH. This reduces venous flow in the medullary and subependymal veins resulting in venous infarction (Figure 2).²⁴

The ventricular index is measured from the falx to the lateral wall of the body of the lateral ventricle; reference ranges for ventricular index according to gestational age are available.²⁵ 4mm over the 97th centile is the 'action line' at which intervention is considered. Recognition of irregular or asymmetric ventricular expansion has led to definition of anterior horn width, measured diagonally (>4mm), third ventricular width, measured in the coronal plane (>3mm) and thalamo-occipital dimension, measured in the sagittal plane (>26mm) as new criteria for PHVD (Figure 3).²⁶

Untreated PHVD is associated with excessive head enlargement. Head circumference increases by about 1 mm daily between 26 and 32 weeks' gestation; between 32 and 40 weeks it increases by 0.7 mm daily.²⁷ An increase of 2mm per day is considered excessive, although this is difficult to detect with certainty over a single day – 4mm over two days, by the same observer, is more likely to be significant.

Management of PHVD

Repeated lumbar punctures (LP) are the simplest way to reduce ventricular size and intracranial pressure. Contrary to experience in adults, due to lower levels of intracranial pressure and open cranial sutures, coning after lumbar puncture is exceedingly rare in neonates. It is best to limit CSF removal to a maximum of 20 mL / kg so as to minimise the risk of cardiovascular disturbance. Unfortunately, LPs are often ineffective, as most neonates have a combined obstructive and communicating hydrocephalus, limiting the volume of CSF available to the lumbar thecal sac. Direct ventricular puncture through the anterior fontanelle represent an alternative method of CSF aspiration; when repeated, however, needle track lesions through the cerebral hemisphere become evident. Repeated LPs or ventricular taps do not reduce the risk of requiring formal CSF diversion, have no effect on neuromotor impairment and are associated with a significant risk of ventriculitis, at 7% in the Ventriculomegaly Trial Group study.^{4,28,29} In practice, once two LPs or one ventricular tap have been necessary to control the ventricular index, insertion of a ventricular access device is preferred.



Figure 2: Coronal ultrasound scan demonstrating right paraventricular intraparenchymal hyperechoic lesion, consistent with haemorrhagic infarction (black arrow). This is likely to progress to a porencephalic cyst.

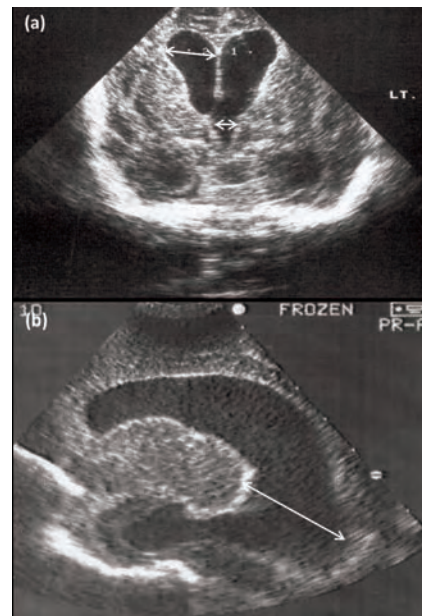


Figure 3: Measurements of ventricular dimensions in the coronal plane (a), denoting the anterior horn width superiorly and the third ventricular width inferiorly (white arrows); (b) defines the thalamo-occipital distance on the sagittal plane (white arrow).

In an effort to control PHVD by reducing CSF production, the International PHVD Drug Trial Group investigated the effects of acetazolamide and frusemide in a randomised trial in 1998.³⁰ Not only did these drugs not lead to an improvement in neuromotor development or CSF diversion requirements, but the data monitoring committee stopped the trial due to worse outcome in the treated group. This was likely related to acetazolamide causing PaCO₂ elevation in ventilator-dependent neonates with chronic lung disease or bronchopulmonary dysplasia and to immature renal function causing acid-base and electrolyte disturbances.³¹

A ventricular access device provides an easy and safe route for repeated aspiration of ventricular CSF with low infection rates.^{32,33} Insertion, through a frontal burr hole, requires a brief anaesthetic in a neurosurgical theatre, and can be safely performed in neonates under 800g. This is a temporising measure, and allows repeated drainage of CSF until the need for permanent CSF diversion can be established. An alternative, but less popular, temporising device is the ventriculosubgaleal shunt.^{33,34} The timing of insertion of a ventricular access device remains controversial. In a retrospective study, early insertion, before crossing the 97th + 4mm ventricular index line, showed lower rates of ventriculoperitoneal shunt.³⁵ The Early versus Late Ventricular Intervention Study (ELVIS) is currently randomising between the two treatment thresholds, with death or shunt dependence and disability at two years the main treatment outcomes.

Drainage, irrigation and fibrinolysis therapy (DRIFT) developed out of an attempt to reduce intracranial pressure and wash out the toxic cytokines from the ventricular system as early as possible.³⁶ The procedure involves

insertion of right frontal and left occipital catheters, with intraventricular injection of tissue plasminogen activator (TPA) that is insufficient to produce a systemic effect. Eight hours after TPA injection, irrigation with artificial CSF is commenced, at 20 mL / hour, under intracranial pressure monitoring, aiming to maintain pressure below 7 mmHg. The drainage fluid clears over about 72 hours, from a dark-coloured thick fluid to straw-coloured CSF.

A recent multi-centre randomised trial recruited 77 infants to DRIFT or standard treatment. Early results did not show any difference in the need for permanent CSF diversion in the DRIFT group.³⁷ However, at two years, severe cognitive disability was significantly reduced in the DRIFT group.³⁸ The median mental developmental index in the DRIFT children was improved by more than 18 developmental points.³⁸ This is the first intervention to demonstrate, within a randomised trial, an improved outcome in infants with PHVD.

The decision to insert a ventriculoperitoneal shunt should not be taken too early. Shunts in this population have a higher rate of failure and infection.^{6,7} It is ideal to wait at least until about term, when the body weight is at least 2 kg, reducing risk of infection and skin ulceration over the shunt. CSF protein should be lower than 1.5 g/L and repeated cultures should be confirmed negative. At this stage, tapping is discontinued. If the head circumference increases by at least 2 mm daily for several days, and ultrasonography confirms this to be related to an increase in the ventricular index, then insertion of a shunt is indicated.

Neurodevelopmental outcome

The prognosis of PHVD depends on the extent of periventricular parenchymal infarction. The rate of cerebral palsy is highest for children who sustained a grade IV haemorrhage and also have a shunt, at 80 to 90%.³⁹ If there are no persistent echolucencies on ultrasonography, 40% of children will develop cerebral palsy and up to 25% will have multiple disabilities.^{29,40} However, the presence of extensive haemorrhagic parenchymal infarction increases the risk of cerebral palsy to up to 80%.⁴⁰

Conclusion

The management of IVH and PHVD remains a significant challenge, and is likely, in the future, to incorporate a combination of mechanical and molecular therapeutic strategies. Close collaboration between neonatologists and neurosurgeons remains central to the development of a safe and effective treatment that maintains CSF circulation and optimises neurodevelopmental outcome. ♦

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Ethical Considerations in Physician-Assisted Suicide



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Physician-assisted suicide (PAS) is a topical issue. Neurology, neurosurgery and rehabilitation medicine are very much at the forefront of PAS as patients who request PAS often have untreatable or terminal neurological conditions. In 2010, the Director of Public Prosecution published the policy on assisted suicide following the lack of prosecution of several cases of those assisting others to die abroad. This article will examine the ethical issues that arise when considering PAS.

Autonomy

Respect for the autonomous wishes of patients was established in common law in 1914 when Cardozo J stated in *Schoendorff v Society of New York Hospital*:

'Every human being of adult years and sound mind has a right to determine what shall be done with his own body.'¹

There is widespread recognition that as long as the patient has the requisite mental capacity, he/she is entitled to make life-limiting decisions with regard to his/her own medical treatment. However, because assistance for suicide is not considered proper medical treatment, the desire to die often goes unheeded during the dying process. The views of philosophers Immanuel Kant and John Stuart Mill on autonomy have contributed greatly to PAS. Kant supported the notion that autonomy should be governed by rational choice,² while Mill asserted that people have a right to self-determination as long as their actions do not harm others.³ Mill emphasised the importance of preferences and desires, rather than rationality. Everyday physicians and patients negotiate treatment goals. Physicians, with their medical expertise, provide advice and recommendations on treatment options. Patients who are experts about their own lives contribute to the collaborative decision-making by expressing their personal preferences and values. A Kantian view of autonomy would support the physician-patient partnership and relational model of decision-making that incorporates mutual respect and reasoned negotiation. The consumer based Millian autonomy emphasises patient preferences and desires, leading to the extension of a patient's right to demand specific interventions which may deviate from established medical standards. Thus, the physician-patient partnership becomes one-sided, with the emphasis on patients' desires and demands.

Which view of autonomy is better? A patient with Kant's view would have to ignore desires and

preferences for pure practical reasoning. This is almost impossible in vulnerable patients because of physical or psychological illness. Indeed, Kant himself argued against the permissibility of self-killing, claiming that it was against moral law to kill oneself even when continued life promised more evil than satisfaction⁴ leading Brassington to suggest that autonomy 'simply peters out at some point before self-killing, so that there is simply no such thing as ... assisted suicide'.⁵ The Millian view allows the patient to regain control over the dying process. However, patients may misunderstand their options for end-of-life care or patients requesting PAS may be depressed or undergoing existential or spiritual crises that confound cognitive clarity and cloud the understanding of end-of-life options.

Both Kant's and Mill's views fail to consider the social context of the patient. An alternative suggestion of a good autonomy model is one that involves an interactive and interdependent approach to decision-making where patients are empowered by family and physicians to consider the values and commitments of all those involved and directly affected by the patients' decisions. Here the key consideration is not whether the patient or physician should be given decisional rights but rather how to improve the autonomous decision-making process of patients within their social context.⁶

Dignity

For many patients, the right to die with dignity means dying without having to suffer from severe physical pain, without being dependent on others for hydration, nutrition and bodily hygiene, and without family and friends having to witness their suffering.⁷

Three concepts of dignity suggested by Schroeder are applicable to PAS.⁷ The first, Kantian dignity, is the intrinsic dignity in every individual rational being with life plans that is an end in itself.⁴ International laws have stressed the inviolability of this human dignity and expanded it to encompass all human beings. Secondly, there is comportment dignity, defined as 'the outwardly displayed quality of a human being who acts in accordance with society's expectations of well-mannered demeanour and bearing'.⁷ Finally, there is meritorious dignity, which builds upon Aristotle's thinking that dignity is something that is deserved rather than inherent and that one deserves it through being honourable.⁸

Killmister simplified the concepts of dignity to

two.⁸ First is the universal Kantian dignity which is the inviolable status one holds simply by being a human being; the other is an aspirational dignity which encompasses both comportment and meritorious dignity because an aspirational sense is contained within both comportment and meritorious dignity. This alliance can be brought together by considering comportment dignity as more to do with the upholding of one's own standards and norms, rather than an upholding of external standards and norms. Therefore, aspirational dignity is 'the quality held by individuals who are living in accordance with their principles'.⁸

Supporters of PAS appeal most closely to aspirational dignity.⁷ Consequently, what standards and principles one has tried to adhere to during life, one may not be able to achieve in death if PAS is disallowed. Opponents of PAS contend that unbearable pain and psychological trauma have no relevance for Kantian-inspired inviolable dignity because such dignity cannot be lost.⁷ Therefore, the intrinsic worth of dignity cannot be diminished in hardship, thus prohibiting PAS.

Personhood

To ensure not being overly burdened by the breadth of moral obligation, many commentators distinguish between 'persons' and 'non-persons' so that we only owe strong moral obligations to persons.⁹ In the Kantian sense, only beings who have the capacity for autonomy or 'moral agency'¹⁰ are persons. Locke defines personhood in a purely psychological sense – a person is '[a] thinking intelligent being, that has reason and reflection, and can consider itself as itself, the same thinking thing in different times and places; which it does only by that consciousness, which is inseparable from thinking, and as it seems to me essential to it'.¹¹ The Lockean concept has largely been superseded by the Parfitian account which, while accepting psychological connectivity, would also consider embodiment in the human brain as a 'background criterion' for personal identity – effectively incorporating physiology into personhood.¹²

Most proponents of personhood would consider anyone in possession of rationality, autonomy and self-awareness as being unequivocally a person.⁹ Rationality and autonomy are more closely allied to the Kantian approach; self-awareness is more closely related to the Lockean/Parfitian concept. Proponents of PAS need to consider whether the right to die is morally defensible. Ford suggests that it is morally difficult to justify the wish to destroy something of ultimate value (life itself).⁹ Ford also argues that it would be possible to separate the person from his/her life

when defining personhood because this conceptual dichotomy would justify the ending of life that significantly lacks value – the so-called 'personhood paradox' in the right to die.⁹

Harris questions Ford's interpretation that ultimate value equates to inviolability.¹³ He argues that in the Kantian sense, by making autonomy central to personhood, it is more important to protect autonomy than physical life itself. Harris also argues that personhood should incorporate a set of capacities for one to value one's own existence – thus when one no longer values one's own existence, it would not be wrong to deprive one of it.¹³ Harris disagrees with Ford's argument of the dichotomy between a person and his/her life when deciding to end life, commenting that it is not life that is being valued, but rather the existence of a particular sort of life that is being valued.¹³ Therefore, one should be allowed to end one's life when one wants to do so.

Sanctity of life

Sanctity of life usually implies inviolability of life. Opponents of PAS describe life as a divine creation and gift, and invoke religious and natural law arguments to protect it before natural death. They also promote medical interventions for the prolongation of life. However, Hume points out that while we may be infringing God's prerogative by taking life and thus altering the divine timing of death, we may similarly be infringing divine prerogative when intervening to save a life.¹⁴

Resistance to PAS is based on the prudential value judgement that life is always better than death. However, life does not necessarily have a presupposed prudential value.¹⁵ Libertarians assert that PAS should be available to any competent adult who wants it. Some advocate a more middle ground approach, supporting the legalisation of PAS but with stringent safeguards.¹⁵

Slippery slope

Keown argues that if PAS is legalised, this will inevitably lead to the acceptance of non-voluntary and involuntary euthanasia because of the loss of 'effective regulation'.¹⁶ Keown also suggests that PAS may initially be regulated as a last resort measure, but eventually become more accepted and preferred.¹⁶ Smith evaluated these arguments in several countries and concluded that there was no concrete evidence to support these claims.¹⁷

Keown states that it is the physician that is the deciding factor in PAS, not the patient. This physician justification could just as easily be applied to situations where the patient cannot make the request, as in non-voluntary euthanasia.¹⁶ Lillehammer's counterargument is

that Keown wrongly implies that only either the physician's opinion or the patient's autonomous choice is required for PAS to be permitted.¹⁸ Lillehammer emphasises that both the physician's judgement and the autonomy interest of the patient are required to provide sufficient justification for PAS to occur.¹⁸ Therefore, the physician does not determine the value of the patient's life; this is done by the patient voluntarily and autonomously. The physician's role is considered to be the beneficence to prevent suffering.

Vulnerable patients

Opponents of PAS feel that vulnerable patients may start to consider death as a possible option for releasing family members, carers and the society at large from the responsibility of having to provide them with care.¹⁹ Furthermore, depression may cloud the view of vulnerable patients.

Proponents of PAS accept the real possibility of abuse of PAS laws. Nevertheless, the mere potential of abuse should not prevent the legalisation of PAS. What is needed are stringent safeguards to minimise or prevent abuse. Physicians should also be trained to spot signs of depression which can occur in terminally ill patients.

Involvement of physicians

Some believe that PAS is contrary to the role and professional duty of physicians. Patients may trust physicians less and be fearful of hospitals if PAS is legalised. Too little trust between physicians and patients could compromise the physician-patient relationship.

In PAS, it would be superficial to say a physician's intent is merely to kill; rather physicians have a duty to ease the suffering of patients, do what is in the best interests of patients and respect the autonomy of patients.

There are concerns that the involvement of physicians in PAS could curtail improvements in palliative and terminal care.²⁰ However, there is evidence that palliative care treatment has in fact improved where PAS is legal.^{21,22} The availability of PAS may also encourage physicians to address other end of life concerns, such as decreasing ability to participate in activities that make life enjoyable, loss of autonomy and loss of dignity, more effectively.²²

Conclusion

It is hoped that this article has provided some fundamental insights into the ethical arguments for and against PAS. It is important that society embarks on a full and informed debate on this issue as it is likely to get more relevant with patients increasingly willing to travel to jurisdictions that allow PAS to seek PAS. ♦

the mere potential of abuse should not prevent the legalisation of PAS

Ethical considerations in physician-assisted suicide: a comment

The Association of British Neurologists has recently sought its members' opinions on physician assisted suicide. The response, available through the ABN's website, was very much (but not unanimously) against. In this article, Dr Sathasivam, a neurologist and ethicist examines the issues.

Dr Sathasivam has written a learned account of the arguments around physician assisted suicide. Through it, we encounter the precision of thinking and clarity of language that characterise the ethicist's approach to such a complex problem. We are reminded, also, of the centuries of careful deliberation on the moral nature of humanity; we should not forget that the definition of autonomy has been debated far longer than motor neurone disease has been recognised. I anticipate that most readers of ACNR will not be aware of the range of arguments that Dr Sathasivam expounds, and will find their own position on physician assisted suicide challenged and nuanced.

Four points in response: first, how does one negotiate a final position on physician assisted suicide, with so many conflicting arguments? How does one choose which 'trumps' which? This is difficult enough as an individual. But it is even more problematic when a group of people, such as the Association of British Neurologists, seeks a consensus. And it is almost impossible to conduct a debate on a nationwide basis. Philosophers have described 'middle ethics', themes common to religious and non-religious worldviews, to assist such enterprises. But more often than not, the lowest common denominator prevails and all that happens is that anecdotal grenades are lobbed from the barricades: pantomime stories of suffering patients

and impotent doctors, of interfering officialdom and scheming families. Curiously, people with a religious view are often dismissed from public debate, as though possession of a settled set of values is a 'prejudice'.

Second, Dr Sathasivam's review fails to include that most philosophical organ: the gut. Sooner or later, as people mull over this or that position on physician assisted suicide, they will find their rationalism bumps up against a visceral 'that's it' or 'that's not right!'. The reasoning behind these colicky interruptions may be unconscious, but deny them at your peril. For so we meet our 'deontological ethical principles' or natural moral law. Somehow these 'bottom lines' need to be captured and respected.

Thirdly, as we consider some patients' requests to die, we should not forget that our responses shape our society as a whole. How do we want neurologists, or the ABN, or England, to be perceived in its approach to illness, dependence and the end of life? And if our position shifts on physician assisted suicide, how would that affect the way society views other suffering, dependent people? Do we edify humanity by allowing physician assisted suicide or do we corrode it?

Finally, for what it is worth, my position is that there are a very few people, in awful irreversible situations, whose request to die has integrity; but the cost of assisting them, to the idea of who a doctor is, what it means to be dependent and, ultimately, to how we revere all life, is simply too great.

Alasdair Coles

ACNR would welcome responses!

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Welcome to the ninth in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to

write short pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.



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Are Antidepressants Dangerous in Epilepsy?

Case

A 24-year-old woman with a history of treatment resistant temporal lobe epilepsy is seen at clinic. She has become significantly depressed. She believes this is partly due to worsening seizure control but also due to strains within her marriage. Her GP has told her that it would not be safe to prescribe an antidepressant. Is his GP right? If not, which class of antidepressant drugs would be best to offer her?

Depression in people with epilepsy is under-recognised and under-treated. There are a number of reasons for this, but one of the most important is the widespread, mistaken belief that antidepressants are unsafe in epilepsy because they lower seizure threshold. In fact, the risks of not treating depression in epilepsy, and the costs in terms of quality of life, far outweigh the slim possibility that antidepressants might worsen a patient's seizures. Yet the British National Formulary (BNF) lists seizures as an adverse effect with most antidepressants and recommends 'caution' in prescribing to people with epilepsy. Where has this idea come from? What evidence is there that, in fact, we should treat depression in patients with epilepsy pretty much 'as usual'? Before considering these questions, and to put them in context, a brief review of depression in epilepsy is useful.

Depression in Epilepsy

Symptoms of depression in people with epilepsy are classified according to whether they occur as brief, self-limiting episodes before, during or after individual seizures, or whether they occur as relatively prolonged episodes of low mood that have no, or a variable, temporal relationship with seizures. It is these latter, 'interictal', depressive episodes that concern us here: episodes of low mood with associated cognitive and somatic symptoms that would in general be recognised as 'significant depression'.

People with epilepsy whose seizures are in complete remission are probably at no greater risk of depression than the general population. But those who continue to have seizures despite treatment undoubtedly suffer high rates of depression and this risk is related to measures of seizure frequency and severity.^{1,2} Among people with the most intractable

forms of epilepsy, depression is undoubtedly very common. For example, in patients with temporal lobe epilepsy undergoing pre-surgical evaluation, around one third will have a history of major depression.³

There are a number of possible causal links between epilepsy and depression^{4,5,6} (Table 1). In most cases, the aetiology is likely to be multifactorial. Some potential causes and mechanisms are specific to epilepsy (rather than to chronic disability per se) and clinically of great importance as they may prompt specific treatment strategies. It is particularly important to remember that depression is a fairly common adverse effect of many anti-epileptic drugs. Phenobarbitone, vigabatrin, levetiracetam and topiramate are especially notable in this respect, but nearly every AED has been implicated. Even antiepileptic drugs with established efficacy as mood stabilisers in bipolar affective disorder will occasionally trigger depression. In some cases the mood disorder appears after seizures are brought under control and may represent part of the spectrum of 'alternating' psychiatric presentations associated with 'forced normalisation'.⁷ This phenomenon can be conceived of as the consequence of removing a biological antagonistic effect of seizures on low mood. Depression is an important complication of temporal lobe surgery for epilepsy, occurring in around one third of patients, especially those with a prior history of depression. Forced normalisation may play a role in this setting too, but depression may occur whether the patient becomes seizure-free after surgery or not. Findings concerning other clinical risk factors for depression in epilepsy have been inconsistent and some risk factors may simply be surrogate markers for severe epilepsy. Temporal lobe epilepsy, for example, is often cited as being especially closely linked with depression, yet a large study that examined a mixed

Table 1: Causal links between Epilepsy and Depression

Depression in epilepsy may be related to:-	
1)	The underlying cause of seizures e.g.: chronic alcohol misuse, structural brain pathology
2)	Possible physiological effects of recurrent seizures e.g.: post-ictal depression, post-ictal exacerbation of depression
3)	Iatrogenic factors <ol style="list-style-type: none"> Antiepileptic drugs temporal lobectomy following seizure control ("alternating" psychiatric phenomena)
4)	Psychosocial consequences of epilepsy <ol style="list-style-type: none"> Generic factors common to chronic disability Factors specific to epilepsy e.g.: Unpredictable nature of seizures, stigma

group of patients with both focal and generalised epilepsy syndromes, all of whom had intractable seizures, found similar rates of depression across epilepsy subgroups.⁸ Psychosocial factors are undoubtedly important. Poorly controlled epilepsy may have a profound impact on social functioning and there is often a compelling relationship between such factors and the onset of depression in individual cases. In this regard depression in epilepsy has much in common with depression in other medical settings. Whether epilepsy is associated with higher rates of depression compared with other disabling illnesses remains uncertain.

No discussion of the causal links between epilepsy and depression would be complete without mention of the recent findings suggesting that a history of depression may actually be a risk factor for epilepsy. This interesting finding has led to speculation that depression and epilepsy may share a common underlying biochemical substrate.⁹ However, there is evidence that alcohol misuse may contribute to this association¹⁰ and other potential mediating factors (eg: structural brain pathology, learning disability) have not been investigated.

Why is depression in epilepsy under-recognised?

Several studies have shown that depression in people with epilepsy is often not recognised by clinicians.^{11,12} There are a number of possible explanations for this. As in other liaison psychiatric settings, depressive symptoms are all too readily interpreted as an understandable reaction to disability. Professionals, even those with specialist experience, can sometimes 'expect' people with a severe illness to be distressed and may consequently fail even to ask about symptoms of depression. A fear of not knowing what to do if a patient does report depression may also contribute. Another explanation for missed diagnoses is that depression in epilepsy may actually present in 'atypical' ways. This intriguing possibility was first documented by Mendez¹³ who estimated that 50% of clinically significant depression in people with epilepsy would fail to meet standard diagnostic criteria. There is now fairly good evidence to support this notion and the term 'Interictal

Dysphoric Disorder' (IDD) has been coined to describe these atypical presentations. These are essentially chronic states of dysthymia with marked irritability whose course is interrupted by brief periods of normality. It is this fluctuation that means such symptoms fail to meet standard diagnostic criteria for chronic dysthymia. There is some evidence that 'IDD' responds to antidepressant treatment but further research is needed to answer key questions in this area. If depression in epilepsy often falls below standard diagnostic criteria, is this because it is not, in fact, clinical depression, simply how people react to their illness and disability? Or is it truly a clinical depression, which responds to conventional treatments, but is unique to epilepsy? Comparisons of depressive symptomatology between people with epilepsy and with other disabling illnesses are required, as are well-conducted treatment trials.¹⁴

Why should we treat depression in epilepsy?

The reasons for treating depression in epilepsy are the same as in any other situation: to improve quality of life and to reduce the risk of deliberate self-harm and suicide. As in other medical illnesses, comorbid depression in epilepsy is linked to poor quality of life and greater disability and there is a firmly established association between epilepsy and suicide. Compared with the general population, patients with epilepsy have a 3-4 fold risk of completed suicide.¹⁵ Not surprisingly, a history of psychiatric disorder is a major risk factor. For someone with intractable epilepsy, depression represents a potentially dangerous double burden.

Antidepressants, seizures and epilepsy

Evidence suggesting an association between antidepressants and seizures arises from a number of sources, each of them flawed as a means of predicting the safety or otherwise of antidepressants taken at therapeutic doses by people with epilepsy.^{16,17} Most of the data concerns the incidence of seizures in people without epilepsy. Thus, provoked seizures are a well recognised complication following overdose with antidepressants and meta-analyses of pre-clinical trials document seizures as a rare but important adverse event with many drugs. Committee for the Safety of Medicines reports are another source of information but subject to reporting bias. In particular, this data cannot be used to compare the relative safety of different drugs: more reports will inevitably be received for the most commonly prescribed drugs that have been in clinical use the longest. The situation in someone with epilepsy is clearly very different. Most importantly, patients with epilepsy will usually be taking anti-epileptic drugs which are likely to have a protective effect with regards any proconvulsant action of antidepressants. What is needed is information about the safety of antidepressants in people with epilepsy.

Here the data, though limited, is in fact very reassuring. Although the numbers of subjects in individual studies is relatively small, the message that antidepressants are well-tolerated in people with epilepsy is clear (Table 2). The largest study to date involved 97 patients with epilepsy prescribed sertraline.¹² Five patients had a possible, transient worsening of seizures and only one patient was thought to suffer a clear deterioration in seizure control. Two studies have even found an anti-epileptic effect of antidepressants in epilepsy.^{23,25}

Table 2

Study	Number of patients	Antidepressant	Effect on Seizure Frequency
Robertson & Trimble, 1985 ¹⁸	45	amitriptyline nomifensine	none
Harmant et al, 1990 ¹⁹	35	fluvoxamine	none
Anderssen et al, 1991 ²⁰	20	paroxetine	none
Hovorka et al, 2000 ²¹	24	citalopram	none
Kanner et al, 2000 ¹²	97	sertraline	Increase in 1 patient Transient increase in 5
Kuhn et al, 2003 ²²	75	citalopram, mirtazapine, reboxetine	none
Specchio et al, 2004 ²³	45	citalopram	Overall decrease in seizures
Thome-Souza et al, 2007 ²⁴	36 (children & adolescents)	sertraline, fluoxetine	Increase in 2

Treating depression in epilepsy

The point at which symptoms of depression are considered significant and should prompt treatment is ultimately a matter of clinical judgement. The decision to treat will be based on an assessment of severity (including the presence of associated somatic and cognitive symptoms) and evidence of impaired general function. Whenever depression is identified in a patient with epilepsy, the risk of suicide must always be assessed.

It is vital that any relationship between the onset of depression and anti-epileptic drug (AED) treatment is identified. When a specific AED is implicated, the drug will usually have to be withdrawn. Sometimes a dose reduction is sufficient but persisting with the AED and adding an antidepressant is rarely, if ever, satisfactory. Most people quite sensibly don't like the idea of taking a second drug to combat side-effects from another. Switching to an AED with mood stabilising (carbamazepine, valproate, lamotrigine) or anxiolytic (pregabalin) efficacy seems intuitively sensible. However, AEDs cannot be switched quickly and although this may be worth considering as a longer term strategy, evidence for this is lacking. Optimised seizure control is, of course, the aim for every patient with epilepsy. For a patient with epilepsy and depression this becomes especially important. If a patient is not under a specialist epilepsy service, referral should be considered. In addition to specialist medical review, such clinics also provide access to support from Epilepsy Nurse Specialists, specialist counselling and service-user groups. As for patients without epilepsy, psychological therapy should be discussed and offered to patients where practical. A therapist with

specialist experience of epilepsy may be particularly helpful.

The pharmacological treatment of depression in epilepsy has been the subject of a number of recent reviews,^{26,27} including a Consensus Statement from the Epilepsy Foundation.²⁸ The choice of antidepressant will be guided by three main considerations: 1) propensity to cause a deterioration in seizure control; 2) drug interactions; 3) side-effect profile. As we have already seen, it is very unlikely that an antidepressant will exacerbate a patient's seizures, but given the variety of antidepressants available today it seems sensible to avoid those that are, probably, associated with a higher risk. For this reason, amoxapine, bupropion, clomipramine and maprotiline are not recommended. Pharmacokinetic interactions are especially likely with hepatic-enzyme inducing AEDs (carbamazepine, phenytoin, phenobarbital) and with enzyme inhibiting drugs (valproate). Most interactions are not clinically significant, a notable exception being the inhibition of phenytoin's metabolism (and consequent rise in serum levels) by fluoxetine. It is good practice to check before prescribing for any patient on polytherapy (i.e. consult the BNF) but such interactions are unlikely at therapeutic doses of citalopram, escitalopram and sertraline (SSRIs), duloxetine and venlafaxine (SNRIs) and mirtazapine (NaSSA). Otherwise the side-effect profile will dictate choice of antidepressant as it does in general psychiatric settings and an associated psychotropic effect, for example night-time sedation with mirtazapine, may be of great benefit for some patients. It is important to discuss the issue of seizure exacerbation with the patient pre-

emptively as the information sheet that comes with their antidepressant is likely to be alarming on this subject and might otherwise lead to non-compliance. Specifically, patients should be reassured that this risk is a theoretical one and that, because they are taking AEDs, they are very unlikely to suffer any worsening of their epilepsy. A 'start low, go slow' approach to the starting dose and rate of dose increments is sensible. If there is a definite increase in seizure frequency or severity a better-tolerated substitute is usually easily found.

So, by way of conclusion, how should we manage the patient described in the clinical vignette at the beginning of this article? A patient with intractable epilepsy presenting with depression should ring alarm bells. We should assess the severity of her depression and carefully consider her risk of self harm. The patient is probably right in her thoughts about aetiology. We should consider factors related to her epilepsy and its treatment, as well as her social circumstances. She has intractable TLE and should be under a specialist epilepsy service. Her current presentation should prompt a review of her epilepsy treatment. The GP was wrong to suggest that antidepressants are unsafe for this patient and it will be important to discuss this point in detail with her. Which antidepressant to choose? An SSRI with minimal potential for interactions (eg: citalopram or sertraline) would be a good place to start. Psychological approaches to treatment should be considered as they would for any patient with depression. Finally, this is a patient we should follow-up carefully; to monitor her response to treatment and to ensure effective liaison with her epilepsy service. ♦

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Handbook of Atypical Parkinsonism

This well presented handbook is a collaboration between authors from Europe, the US and Canada. Its editors and contributors are major experts in the field of parkinsonism. It is a well presented, handbook-size textbook focusing on differential diagnosis and clinical aspects, backed up with scientific rigor. It is largely aimed at specialists in the field of movement disorders, although would be of interest to general neurologists and geriatricians. It would be an invaluable resource for anyone undertaking a clinical review or preparing a case presentation needing to know more detail about the specific disorders.

The book opens with a fascinating preface by John Steele of Steele-Richardson-Olszewski fame, with a brief review of the history of atypical parkinsonism. The chapters then take the reader through an introduction to the differential diagnosis of parkinsonism, chapters on Parkinson's disease itself and the spectrum of Lewy Body disease, multi-system atrophy, progressive supranuclear palsy, cortico-basal degeneration, other causes of parkinsonism, the clinical approach to the differential diagnosis of parkinsonism and then a review of non-pharmacological treatments for atypical parkinsonism.

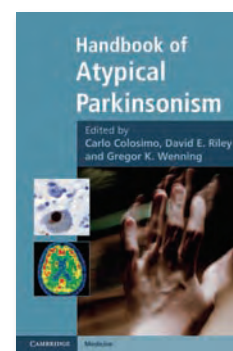
Overall, the book is well presented, with clear text and very clear and useful tables and illustrations. The introduction usefully categorises atypical parkinsonism into synucleinopathies and tauopathies and provides a very helpful aide memoir table summarising the frequent clinical features of all the conditions. The chapter on Parkinson's disease and the spectrum of Lewy Body disease emphasises the overlap between dementia with Lewy Bodies and Parkinson's disease dementia in particular. This chapter is especially well constructed, taking the reader through the history, clinical findings, natural history, laboratory investigations, genetics, pathology, management and conclusions about the spectrum of disorders. This neat structure is unfortunately not applied in exactly the same way across

all chapters, although each subject area is covered in similar detail. The information is up-to-date, with references taken right up to 2010.

The chapter on multi-system atrophy is well constructed. There is a particularly helpful account of possible investigations and imaging and an excellent summary of pragmatic management at the end of the chapter. The chapter on supranuclear palsy is again detailed and there is a comprehensive table on alternative causes of supranuclear palsy associated with parkinsonism. The overlap between the pathological features of PSP and cortico-basal degeneration is emphasised. The section on the treatment of PSP is rather brief and does not mention palliative care issues or management of falls, although these principles are covered in the review of non-pharmacological treatments in the last chapter of the book. There is an excellent chapter summarising cortico-basal degeneration and its clinical features, the movement disorder and cognitive dysfunction in this condition. There is an expansive review of other causes of parkinsonism including an exhaustive list of drugs reported to induce parkinsonism, toxic, metabolic, infective, structural and degenerative causes.

The final chapter on the non-pharmacological treatments covers the broad spectrum of treatments that may be employed in these conditions, in view of the great lack of effective pharmacological therapies. This chapter is particularly well constructed and will appeal to those who manage these conditions in their daily practice. The management of balance and falls, the roles of physiotherapy and occupational therapy and the role of speech and language therapy in dysarthria and dysphagia are all covered.

I think this book is a useful addition to the field and is particularly appealing because it is clinically orientated but of sufficient detail to provide interest and new information to specialists in the field. Its size makes it very transportable and its structure makes it very readable and accessible. ♦



Editors: Carlo Colosimo, David E Riley and Gregor K. Wenning
Publisher: Cambridge University Press March 2011
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ISBN: 9780521111973

Reviewed by:
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Duchenne Muscular Dystrophy or Meryon's Disease Second Edition

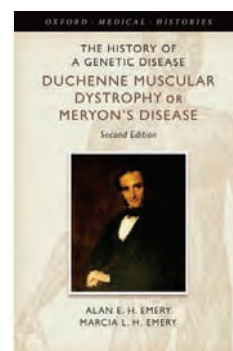
This short book is a pleasure to read. Professor Alan Emery has for some time been a champion of Edward Meryon, one of the hitherto unsung heroes of Victorian medicine. The Emerys' thesis is that Meryon, rather than Duchenne, should be credited with the first comprehensive clinical description of this disease together with some important pathological observations. Through their efforts, Meryon is now included in The Oxford Dictionary of National Biography and his former home, 14 Clarges Street, Piccadilly, has acquired a blue plaque. The book, however, is much more than a biography and a monograph of a muscle disease: it is a fascinating account of general medical history and the development of medical scientific thinking.

Meryon's seminal paper on muscular dystrophy was given to The Royal Medical and Chirurgical Society in 1851. Having excluded spinal cord pathology, he provided microscopic pathology of diseased muscle the following year "the striped primitive fibres were found to be completely destroyed, the sarcous element being diffused, and in many place converted into oil globules and granular matter, whilst the sarcolemmma...was broken down and destroyed". Duchenne's description of "Paralysie hypertrophique de l'enfance" came in publications in 1861 and 1868 with further detailed descriptions by Gowers (of the manoeuvre) in 1879.

After the initial detailed clinical descriptions, there

followed work on nosology, with the recognition of other muscular dystrophies, including limb girdle, FSH, and Becker dystrophy. The authors stress that investigation and ideas often became dead ends because of lack of supporting science. Genetic breakthroughs came with knowledge of Mendelian inheritance and then the Lyon hypothesis, with the X-linked inheritance of DMD being confirmed by segregation analysis finally in 1959. Other important advances were the availability of serum CK analysis in 1959 (itself a fascinating story) and the use of Bayesian statistics in genetic counselling in 1964. Better electron microscopy supported the "leaky muscle membrane" theory. The major breakthrough in understanding came with the use of recombinant DNA technology and the use of RFLPs leading to the isolation and sequencing of the gene and the identification of the gene product, dystrophin, between 1985 and 1987. The final section deals with potential advances in treatment, an optimistic area.

The book is highly readable. It emphasises the cult of the individual in early pioneering studies, the importance of encouragement and mentorship of individual researchers by some of the giants of medicine and, above all, of serendipity. It will be of interest to anyone working in the field of myology and anyone with an interest in the history of medicine. ♦



Authors: Alan EH Emery & Marcia LH Emery
Published by: Oxford University Press.
Price: £80.00
ISBN: 978-0-19-959147-3

Reviewed by:
 Bryan Lecky, The Walton
 Centre for Neurology &
 Neurosurgery NHS
 Foundation Trust, Liverpool.

Introduction to Clinical Neurology (4th Edition)

Unusually small for a neurology textbook, this compact 504 page paperback is a gem for those looking to grasp the key concepts of clinical neurology. Those more used to heavy-weight tomes should not be fooled into thinking this little book lacks content; all 19 chapters are relevant to the bedside practice of neurology. Aimed at medical students and junior doctors, the author successfully demystifies neurology in a refreshingly direct way based on well explained general principles and a clear and systematic approach. This newly printed fourth edition has the same format as its predecessors but incorporates clinical updates from the past five years.

The opening section, entitled The Basic Approach, should be compulsory reading for all medical students. It starts with a discussion of the principles of anatomical localisation in which the London Underground analogy (featured on the cover) is introduced. This is followed by chapters two and three about the neurological examination and pathology.

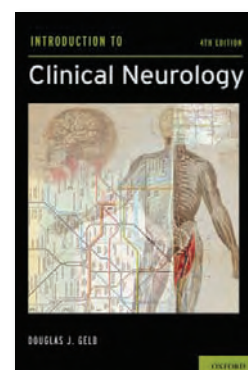
The underground theme is useful. It provides means of conveying concepts of lesion location; the lateral medulla would have to be Kings Cross; single-line but centrally located stations (Goodge Street perhaps) might represent important but anatomically uncluttered structures like the internal capsule. This sort of thing can explain a seemingly impenetrable subject in the time it takes for a cold drink to be consumed.

In the second section (Common Diseases), the author describes the disorders seen most often in clinical practice with chapters on stroke, seizures, neuromuscular disease, dementing illnesses, movement disorders, sleep disorders, and multifocal central nervous system disorders. Section 3 is entitled Common Symptoms and includes chapters on acute mental status

changes, headache, visual symptoms, dizziness and disequilibrium, back pain and neck pain, and finally incontinence. Two chapters (paediatric neurology and geriatric neurology) and some practice cases make up the final section, entitled Bookends. The neuromuscular disorders, dementia and headache chapters are particularly good, providing a comprehensive overview of the topics, with useful illustrations and memorable mnemonics. Case scenarios are included in all chapters. Detailed descriptions of aetiology are provided but the focus is on the information relevant to the investigation and management of the patient. Some conditions, such as metabolic diseases, are omitted, as the author states these are easily found in other general text books. Highly specialised information, such as the details of specific treatments is often intentionally omitted: this could be frustrating for the more senior medic but is keeping with the emphasis of the book on the generic approach to neurology.

Once into the book, it is a fairly easy read. As with most books some sections heavier going, with relatively few illustrations. Detailed medication tables are provided for headache and epileptic medications, which are very useful, however, as with the rest of the book, the information provided relates to American medical practice, which British readers should bear in mind.

As a final year medical student (CF) looking to consolidate knowledge before finals, this book provided a comprehensive overview of the common neurological disorders but its particular appeal was to provide a detailed grounding in the basics of how to think diagnostically. Shame about the loss of white coats: it would have fitted nicely in the pocket! ♦



Author: Douglas J. Gelb
Published by: Oxford University Press
Price: £32.50
ISBN: 978-0-19-973484-9

Reviewed by:
 Charlie Florance,
 Final Year Medical Student
 Cardiff University and
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 University Hospital of Wales.

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MS Frontiers: bring the research community together to beat MS

Conference details: 23-24 June 2011, Sofitel, London, UK. **Reviewed by:** Susan Kohlhaas, Research Communications Manager, MS Society.



Delegates gather at the MS Frontiers poster session to discuss their work.



Professor Alastair Compston receiving the Ian McDonald Memorial Plaque from Tony Kennan, chairman of the MS Society.

In June of this year over 300 delegates from around the world gathered at the Sofitel in London Heathrow for MS Frontiers, the MS Society's biennial conference for researchers, clinicians and health care professionals. Events such as MS Frontiers are vital in bringing the research community together to share their work and thoughts about the future of MS research.

Topics for this year's event included plenary sessions on stem cells, clinical trial design and a debate on the causes of MS.

Day one of the conference started with a plenary session on stem cells. Professor Robin Franklin from the University of Cambridge spoke about utilising the power of the brain's own stem cells to repair damage to myelin. Professor Mark Freedman, based at Ottawa Hospital Research Institute, presented his work on using hematopoietic stem cells as a potential treatment for people with MS. The two presentations highlighted very different approaches to using stem cells as a treatment approach for people with MS.

Breakout sessions for the day featured topics as varied as immunology and therapies of MS, advances in imaging and biomarkers, health economics and patient reported outcome measures and symptom management, care and support. These were followed by a poster session at which around 50 delegates presented their work.

After the poster session, delegates gathered together for a debate on the causes of MS. Professor Sir Andy Haines of the London School of Hygiene and Tropical Medicine

chaired the session with contributions from a highly esteemed panel including; Professors Alastair Compston of the University of Cambridge, George Ebers of the University of Oxford, Gavin Giovannoni of St. Bart's and the London School of Medicine and Dentistry as well as Dr Paul Bull, an MS Society Research Network Member. The debate focused on different genetic and environmental factors associated with MS.

Professor Compston spoke about the genetic element to MS, including details of the latest research identifying new genes associated with the condition that are known to influence the immune system. Professor Ebers spoke about evidence suggesting a potential role for vitamin D deficiency in the development of MS. Professor Giovannoni spoke about the potential role of Epstein Barr Virus in the development of MS and Dr Paul Bull gave a personal perspective on his experiences of MS.

Day two of the conference began with parallel sessions on genes and environment, protecting and repairing the nervous system, and innovations in symptom management, care and support.

Following on from the parallel sessions was a plenary session on clinical trial design. Dr Jeremy Chataway from Imperial College NHS Trust spoke about a new seamless adaptive trial design and how it is being applied in a new trial called MS-STOP. Professor Rona Moss-Morris of the University of Southampton presented results from a trial on cognitive behavioural therapy to facilitate adjustment

to MS. Finally Professor Peter Thomas and Dr Sarah Thomas from Poole Hospital NHS Foundation Trust presented results from a randomised controlled trial assessing the effectiveness and cost-effectiveness of a group-based fatigue management approach. All three presentations focussed on different approaches to clinical trials in MS research and were well received.

The Ian McDonald Memorial Lecture was delivered by Professor Alastair Compston of the University of Cambridge and was one of the highlights of the two day conference. Professor Compston spoke about four ages of MS research including; the age of awareness, the age of description, the age of enlightenment and a time for solution.

He gave a historical overview of MS research and highlighted contributions that Ian McDonald and colleagues have made to the field over the years. He particularly focused on clinical trials of alemtuzumab in patients with MS, improvements in our understanding of the neurobiology of MS and advances in our understanding of the genetics of MS. He concluded that these advances have brought us to a time for solution in MS research.

In summary, MS Frontiers 2011 allowed delegates the chance to hear about cutting edge advances in MS research and discuss their present work with researchers and professionals in the field and form important collaborations that will lead to advances in the treatment and care for people with MS in the future. ♦

Alzheimer's Association International Conference

Conference details: 16-21 July 2011, Paris, France. **Reviewed by:** Basil Ridha, Department of Neurology, Brighton and Sussex University Hospital, Brighton.

Compared to last year's 2-day flight to exotic Honolulu, AAIC this July was only a 2.5-hour train ride to Paris from London. About 5,000 researchers gathered to discuss every aspect of Alzheimer's disease (AD) from molecule to global impact with over 15 plenary presentations, and 350 oral and 1800 poster presentations; a tribute to the 36 million AD sufferers worldwide.

The conference was preceded, as usual, with a one-day Imaging Consortium, discussing the latest from MRI and PET imaging, particularly their role in diagnosing AD at a very early or presymptomatic stage. Professor Karl Herholz from Manchester University gave an overview of the different fluorinated amyloid ligands which could potentially have a clinical role in diagnosing AD. Professor Clifford Jack from the Mayo Clinic demonstrated that the reduction in CSF A β 42 was upstream from elevated CSF tau or hippocampal atrophy.¹ This and numerous other presentations supported the model proposed by Jack et al relating dynamic change in various biomarkers with disease stage.²

The main conference was again dominated by biomarkers in AD. There is now even stronger evidence for the role of structural and functional MRI, amyloid PET imaging and CSF biomarkers in the diagnosis of AD at an earlier stage and identifying normal subjects with positive biomarkers, who are at higher risk of developing AD. Numerous presentations identified potential novel CSF and serum biomarkers of AD such as soluble APP in the



CSF and A β 42 in the serum.

Interesting work was presented on the pathophysiological role of intraneuronal rather than extracellular A β deposits. In his plenary presentation, Dr Hiroshi Mori from Osaka City University showed that in cases of AD due to the Osaka APP mutation, there is intracellular accumulation of A β oligomers in the absence of extracellular A β plaque deposition. Drs Oliver Wirths from the University of Göttingen and Benoit Delatour from Paris, showed the pathogenic role of intraneuronal A β in AD mouse models.

Genome wide association studies have so far identified ten genes implicated in late-onset AD. The recent establishment of the International Genomics of Alzheimer's disease will provide an unprecedented opportunity to identify their interaction with the environment and other candidate genes.

An impressive symposium was dedicated to the preliminary findings from the 150 participants so far recruited into the Dominantly

Inherited Alzheimer Network. Imaging and CSF biomarkers suggest changes can be detected over 10 years prior to the onset of dementia.

Regarding therapeutics, Dr Eric Siemers from Eli Lilly, showed in his plenary presentation that treatment with Semagacestat, a gamma secretase inhibitor, caused worsening cognition in the treatment arm, resulting in the early termination of the IDENTITY study. Another highlight was the systematic review of the Amyloid Imaging Related Abnormalities (ARIA) seen in clinical trials involving amyloid lowering agents. ARIA was sub-classified to ARIA-E implying vasogenic oedema and / or sulcal effusion seen on FLAIR sequences, and ARIA-H implying haemosiderin deposits (microhaemorrhages and superficial siderosis) seen on T2* sequences.³

The most unique highlight of the AAIC-2011 was President Nicolas Sarkozy's address to the conference highlighting the commitment of French leadership to providing comprehensive care for all AD sufferers in France and encouraging research into AD following the launch of the French National Alzheimer's Plan in 2008. ♦

1. Jack CR et al. Evidence for Ordering of Alzheimer Disease Biomarkers. Arch Neurol. 2011;
2. Jack CR et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9(1):119-28.
3. Sperling RA et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011 Jul;7(4):367-85.

PREVIEW Modern Thinking in MS Management Educational Meeting for Consultant and Registrar Multiple Sclerosis Specialists

Conference details: Friday 24th (evening) and Saturday 25th February 2012, Crowne Plaza NEC Hotel, Birmingham Airport.

On behalf of Teva Pharmaceuticals Ltd, I would like to invite practicing Multiple Sclerosis specialists to the national educational meeting 'Modern Thinking in MS Management'. This meeting will bring together 100 Consultants and Registrars from across the UK to provide a platform for discussion to explore and review current and future management of MS.

With well established and emerging therapeutic options for MS treatment, this timely forum will allow delegates the opportunity to interact with a faculty of high calibre specialists, reviewing strategies through lively debate and informative discussion, in order to provide the most appropriate management of today's and tomorrow's MS patients.

The meeting will be chaired by me, Professor David Bates from the University of Newcastle, and Dr David Cottrell from the University of Bristol.

Event highlights include:

- Scientific plenary sessions led by renowned MS experts
- Debates around early diagnosis and treatment and current guidelines
- Review of current hot topics
- Patient case studies
- Interactive workshop sessions
- Developments and trends in MS diagnosis and management

To register your interest for this meeting:

Please email your name, job title, institutional affiliation and postal address to modernthinking@apothecon.com. Please note that places for the meeting are limited and you will be contacted in due course if you have a place to confirm at the meeting.

We do hope that you are able to join us for this important review of current treatment and a look at the future of MS management. The 'Modern Thinking in MS management'



meeting promises to be an exciting, stimulating and informative event.



Professor David Bates
Professor of Clinical Neurology,
University of Newcastle upon Tyne

CME accreditation is being sought.
This meeting is initiated and funded by Teva Pharmaceuticals Limited.
a. C0911-743
b. Date of preparation: October 2011

TNA UK Annual Conference / AGM and 2nd Study Day for Healthcare Professionals

Conference details: 18th June 2011, Grand Connaught Rooms, London, UK. **Reviewed by:** Jillie Abbott, Chairman, Trigeminal Neuralgia Association UK.



TNA UK Display Stand.



Delegates listening to the presentations.

TNA UK held their 2nd Study Day for Healthcare Professionals alongside their patients' conference and AGM on Saturday 18th June in London. The day was a great success for all those that attended, with healthcare professionals coming from as far as India, Jordan, Germany and Holland and members and carers coming from all over the UK.

The numbers attending were: Patients' Conference, 94 TN sufferers plus 41 carers; Study Day, 41 healthcare practitioners.

The Study Day had accreditation from the Royal College of Physicians (London), the Royal College of Anaesthetists and verifiable CPD for dental practitioners.

During the members' conference, presentations were given by specialists in oral medicine, consultant neurosurgeons and neurologists as well as Chair of the TNA UK's Medical Advisory Board, Professor Joanna Zakrzewska. Talks ranged from: Getting the Right Diagnosis, Choice of Medication, Surgical Options, Going to the Dentist, and Getting a Better Quality of Life. These talks were then followed by a combined Q&A session that went two ways. Firstly, questions to the specialists and then questions from the specialists to the patients. A greater understanding of TN and its management was gained by both sets of attendees.

Carers were also able to discuss the impact of TN with one another and those suffering from the condition. All carers were asked to complete a detailed, 8-page questionnaire, and all those with TN and/or facial pain participated in a lengthy (15-page) survey about their condition. These results will all be analysed by TNA UK, providing vital statistical data for future research.

Information was readily available in the form of leaflets and books from the TNA stand

as well as from stalls manned by volunteers from the Migraine Trust, Migraine Action and Carers UK.

The study day, that was held alongside the Conference, started with a moving account from a TN sufferer about how the condition had changed her life, "Living with Trigeminal Neuralgia". Many attendees thought that this contributed to being one of the most important things that they learnt from the day, for example feedback forms stating "patient's perspective very educational". The majority of participants commented that the patients' involvement during the whole day was one of the aspects they most liked about the study day.

This was followed by a wide ranging programme:

Common causes of unilateral facial pain
Dr Alex Crighton

Trigeminal autonomic cephalalgias and patient histories – Dr Manjit Matharu

Trigeminal neuralgia aetiology, diagnosis and investigations
Prof Joanna Zakrzewska

Impact of TN on quality of life and management – Dr Frances Cole

Medical management
Prof Joanna Zakrzewska

Discussion Panel

When to refer, decision making - patient, GP, specialist – Patient / Dr Frances Cole / Prof Joanna Zakrzewska

Surgical therapies for TN and discussion
Prof Hugh Coakham / Mr John Wadley

Support groups, giving explanations
Ms Jillie Abbott / Prof Joanna Zakrzewska

Quiz on TN – Prof Joanna Zakrzewska

The day ended with the study day attendees joining the TNA members for the interactive Q&A Panel discussion. This resulted in lively debates on a wide range of questions and comments from both sides.

All participants completed evaluations and these all rated the overall study day as over 4 (scale 0-5) and included comments such as:

"Very well organised conference, interesting titles and authors. Congratulations. Thank you very much."

"Multidisciplinary panel and patient involvement were the two aspects of the course that I most liked."

"Excellent lectures, very informative and up to date."

"Clear, well argued discussion of evidence-based care."

DVDs of the study day showing all the speakers and their PowerPoint presentations are now available at a cost of £40 and can be ordered from:
TNA UK, PO BOX 234, Oxted, RH8 8BE

Further information on the Trigeminal Neuralgia Association can be found at:
www.tna.org.uk



The prion hypothesis of neurodegenerative disease spreads

Over recent years there has been an increasing interest in the idea that the key pathological species of protein that characterise certain neurodegenerative disorders may cause disease through a prion like process. This new theory posits that the intracellular protein aggregation spreads from cell to cell and that this then seeds pathology in the cell it has affected, in a fashion similar to that proposed for prion protein in the spongiform encephalopathies. The evidence that this is the case has been slowly accumulating, although the attractiveness of the theory has often led to speculation ahead of the actual data.

Two recent papers have now added more weight to the theory. In the first of these papers, the laboratory of Virginia Lee has shown that a variety of alpha-synuclein fibrils can enter neurons via an endocytic pathway and promote recruitment of soluble endogenous alpha-synuclein. This recruitment then leads to the development of insoluble Lewy bodies and neurites, so showing that alpha-synuclein can be taken up by neurons and seed pathology. This pathology that they see in vitro, not only resembles that seen in PD, but it also leads to neuronal dysfunction and death. This is an important study because until now it has been shown that alpha-synuclein can spread from cell to cell, but has not been shown to induce any pathology. However whilst this paper provides an additional important element to the story, it should be realised that all the studies were done in vitro.

The second study is in the field of amyloid and Alzheimer's Disease (AD). In this study the authors show that injecting AD brain extracts into animals could induce amyloid pathology at sites distal to the injection, and that this accumulation increased with time and did not occur in the absence of the inoculum. As with the study above, it again shows that pathological proteins can spread between nerve cells and induce pathology and that this may be one of the key events in how neurodegenerative disorders evolve. Of course whether this occurs in people with these diseases remains unproven, as does how one could interfere with this process if it were shown to be the case.

– Roger Barker.

Volpicelli-Daley LA et al (2011). Exogenous α -synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. NEURON 72:57-71.

Morales R et al (2011). De novo induction of amyloid- β deposition in vivo. MOL PSYCHIATRY. epub Oct 4 2011.

Can I take my blue inhaler for my congenital myasthenia please, doc?

Well not quite, yet. Yes, we are talking of a very rare condition, which most general neurologists may never encounter in their life time. However, the awareness of rare syndromes has always fascinated neurologists. How many clinicopathological conferences have we sat through discussing the features of Histiocytosis-X, Alexander's disease and POLG mutations? But nothing is better than knowing that a reasonably safe and cheap drug may be available for a genetic condition, albeit rare. Congenital myasthenic syndromes are indeed rare. Even in a specialist neuromuscular clinic you only have a handful of each of these mutations. However, more and more mutations are being identified and it is extremely useful to know that once the diagnosis is made, the treatment response is different for different mutations.

Most patients with a synaptic AChR deficiency respond

reasonably well to pyridostigmine. On the other hand, Pyridostigmine is ineffective and potentially worsens the condition in those patients with endplate acetylcholinesterase deficiency (COLQ mutation), slow channel syndrome (where kinetic defects cause the channel to close very slowly), DOK7 and beta-2 laminin mutations. Patients (especially those with DOK7 mutation) may present in adult life and can be mistaken for seronegative myasthenia (Alseth et al 2011).

A recent open-label intention-to-treat study on patients with COLQ (n=3) or DOK7 (n=15) mutations has shown that beta-2 adrenergic agonist albuterol (US name for Salbutamol) was beneficial (Liewluck et al epub). Patients had improvement in their walking and climbing distance with corresponding reduction in their disability scores (all $p < 0.0001$). The systemic dose used was from 4 to 12 mg/day in adults (An inhalation of standard salbutamol only delivers 100mcg per puff). The effect was persistent despite continuous use and improved the quality of life in all patients, with some patients becoming more independent and even symptom-free.

This is confirming the studies looking into other beta-2 agonists ephedrine and salbutamol in DOK7 or epsilon-subunit mutations (Lashley et al 2010, Sadeh et al 2011). We have known that sympathomimetics working through the beta-2 receptors are useful in myasthenia since the 1930s. What we don't know is how they influence the neuromuscular transmission. Further prospective controlled trials should tell us whether the beta-2 agonists (taken systemically for the time being) are useful in this rare genetic condition.

Recently new mutations have been identified in the GFPT1 gene in patients with congenital myasthenia phenotypically similar to the DOK-7 mutations – i.e. limb girdle weakness with minimal ocular or facial involvement (Guergueltcheva et al epub). These patients have been given the term congenital myasthenia with tubular aggregates (CMS-TA) in view of their muscle biopsy findings. With new mutations being identified regularly, it might not be too far before inhaled bronchodilators are carried around by some of the congenital myasthenic patients, provided we can ensure adequate systemic absorption.

– Dr Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, Edgbaston, Birmingham.

Alseth EH, et al. Investigation for RAPSN and DOK-7 mutations in a cohort of seronegative myasthenia gravis patients.

MUSCLE NERVE. 2011 Apr;43(4):574-7.

Liewluck T, Selcen D, Engel AG. Beneficial effects of albuterol in congenital endplate acetylcholinesterase deficiency and Dok-7 myasthenia. MUSCLE NERVE. 2011 Sep 19. doi: 10.1002/mus.22176.

[Epub ahead of print]

Lashley D, et al. Ephedrine treatment in congenital myasthenic syndrome due to mutations in DOK7. NEUROLOGY. 2010 May 11;74(19):1517-23.

Sadeh M, Shen XM, Engel AG. Beneficial effect of albuterol in congenital myasthenic syndrome with epsilon-subunit mutations. MUSCLE NERVE. 2011 Aug;44(2):289-91.

Guergueltcheva V, et al. Congenital myasthenic syndrome with tubular aggregates caused by GFPT1 mutations. J NEUROL. 2011 Oct 6. [Epub ahead of print]

Expansion of the chromosome 9 story in FTD-MND: C9ORF72

Since the discovery of SOD1 in 1993, many more monogenic causes of autosomal dominant Motor Neurone Disease (MND) have been identified. Between them these account for only a quarter of all familial cases, and few sporadic cases, and so their

clinical significance has been limited. The overlap between Fronto-Temporal Dementia (FTD) and MND, most strikingly in autosomal dominant FTD-MND kindreds, has raised the possibility of shared mechanisms and genes. This new gene was located in a step wise fashion using ever more advanced genetic detective work, much of it by these authors. Linkage analysis of kindreds with autosomal dominant MND-FTD from Finland, Europe, the USA and Canada had identified the short arm of chromosome 9 as a region of interest. Genome wide association studies (GWAS) and analysis of linkage disequilibrium narrowed this down to 9p21. Both papers describe finding the repeat by sequencing this area of interest in kindreds known to have 9p21 linked disease. They independently identified a hexanucleotide repeat mutation in a non-coding region of C9ORF72, a gene of unknown function that is highly conserved across species. Both state that this new mutation is the commonest monogenic cause of MND-FTD identified to date.

Renton et al focus on making persuasive arguments for the pathogenicity of this mutation, demonstrating co-segregation and significant association of the mutation with disease in known and newly identified kindreds with 9p21 linked MND/MND-FTD, and absence of the mutation in both matched and genetically diverse controls. The co-incident discovery of this mutation by DeJesus-Hernandez et al, published in the same volume of *Neuron*, and both groups' finding of large repeat sizes in expanded repeat carriers, add weight to their claims.

DeJesus-Hernandez et al suggest that this mutation may cause disease by impacting transcription of one of the three splice variants of the C9ORF72 gene. They found reduced variant 1 expression in frontal cortex and lymphoblasts in cases with the expanded repeat. They cite previous work showing that expanded repeats in noncoding regions can cause disease by generating RNA foci in affected cells. They demonstrate the presence of these foci in the frontal cortex and spinal cord or 25% of carriers of this repeat, but only 1% of noncarriers, suggesting a mechanistic overlap with other noncoding repeat expansion disorders including the myotonic dystrophies and several of the spinocerebellar ataxias. The same type of disease causing mutation, an intronic hexanucleotide repeat expansion, is known to cause RNA gain of function in SCA36, a genetic ataxia with motor neurone involvement sharing clinical features with MND.

This joint finding has immediate clinical significance in that it would allow improved diagnostic, predictive and prenatal testing in individuals at risk for familial MND-FTD, and is clearly relevant to sporadic cases also. There are the general benefits of new therapeutic targets and further insight into the pathogenesis of these devastating diseases, and of other multinucleotide repeat disorders.

These papers complement each other well, gaps in one being addressed in the other, but questions remain. Renton et al describe two controls with a repeat number thought to be pathogenic were identified but not mentioned further. Why some cases had MND only, some FTD only, and some MND-FTD, is not yet addressed. DeJesus-Hernandez et al describe comparative clinical data for carriers presenting with ALS and those with FTD, and no striking disparities are found, though they do not directly compare repeat lengths between the two groups. There is much more work to follow, but for now these papers describe an exciting step forward in understanding the genetics and pathogenesis of MND and FTD, and the links between them.

– **Ailbhe Burke, Academic Clinical Fellow in Neurology, National Hospital for Neurology and Neurosurgery, Queen Square.**
DeJesus-Hernandez et al (2011). Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. NEURON 72 (2):245-256.
Renton et al (2011). A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. NEURON 72 (2): 257-268

Stem cells come of age

There has been a revolution in the world of stem cell biology in recent years as the ability to steer cells to different fates becomes better understood. This includes the capacity to re-programme adult somatic cells to pluripotent stem cells (iPS cells) and then last year it was reported that adult somatic cells could be turned directly into neurons. This paper was initially met with some scepticism but subsequently a number of other groups have reproduced this finding, and of late this has been taken a stage further by making dopaminergic neurons from skin fibroblasts without the need of going through an iPS stage.

This direct generation of functional dopaminergic neurons has now been reported in a series of papers from different groups, using slightly different approaches. However, the ability to do this seems robust and has obvious implications for Parkinson's Disease (PD). Firstly it could allow for the study of dopaminergic neurons in vitro as a means of studying the disease process in an individual and those same cells could then be used for drug screening. Secondly, this approach could be used to generate autologous transplantable dopaminergic neurons for patients with PD, which avoids immunological and ethical concerns as well as issues on tumour genesis.

These papers reveal something of the speed that new technologies can advance and whilst much still needs to be done, it gives great hope to all those involved in disease modelling and therapeutics.

– **Roger Barker.**

Caiazzo M et al (2011). Direct generation of functional dopaminergic neurons from mouse and human fibroblasts.

NATURE. 2011 Jul 3;476(7359):224-7.

Pfisterer U et al (2011). Direct conversion of human fibroblasts to dopaminergic neurons.

PROC NATL ACAD SCI USA 2011 Jun 21;108(25):10343-8.



Winter Meeting

**Institute of Child Health
January 11th – 13th 2012**

Programme

- 11th January

Symposium: Recent advances in understanding brain tumours – Chair Professor Silvia Marino

Dorothy Russell Lecture: Relevance of molecular markers for brain tumour diagnostics – Professor Andreas Von Deimling, University of Heidelberg, Germany

- 12-13th January – Meeting

Programme Secretary:

Dr Federico Roncaroli, Imperial College, London
 Tel. +44 (0)20 331 17178
 Email f.roncaroli@imperial.ac.uk

More information on the Website of the British Neuropathological Society www.BNS.org.uk

ENS and EFNS Agree to Merge the Two Societies

The first meeting between representatives of the European Federation of Neurological Societies (EFNS) and the ENS took place during the 13th Congress of the EFNS in Florence, Italy, September 12-15, 2009. Jacques De Reuck, President of the EFNS, and Richard Hughes, President-elect of the EFNS, met with ENS President José Ferro and ENS Secretary General Gustave Moonen, in order to discuss the basis for a cooperation in the future between these two major European neurological societies. A task force involving six representatives, plus members of the administrative secretariats, of the EFNS and the ENS was subsequently created in order to work out a concept of cooperation between the two societies. Progress has been rapid in the past two years, culminating in a historic moment which took

place during the 15th Congress of the EFNS in Budapest, Hungary, September 10-13, 2011.

Zohar Argov (ENS President) Richard Hughes (EFNS President) Gustave Moonen (Secretary General ENS) Detlef Kömpf (Secretary General EFNS) signed an Agreement during the opening session of the Budapest Congress of the EFNS to merge the two societies to form a unique organisation designated as the European Academy of Neurology (EAN). From 2015 onwards all activities of the ENS and EFNS shall be accomplished exclusively by the EAN. Until then the ENS and EFNS will appoint members to the Transition Task Force of the EAN.

For more information see www.ensinfo.org

New upright microscope for advanced clinical research

Nikon Instruments has launched the Eclipse Ni-U. Designed with core technology used in Nikon's renowned Eclipse Ti inverted research microscope concept, the manual Ni-U is designed to meet the needs of all advanced bioscience and clinical research. The flexibility provided by motorisation capability and multi-mode operation, combined with high optical quality as well as improved ergonomics, provide access to all the major imaging techniques and observation methods.

Nikon's proprietary stratum structure has now been incorporated in this upright microscope. The structure enables optical paths in two tiers, providing complete flexibility with efficient system configurations and custom combinations according to application. A choice of stackable turrets is available for epi-fluorescence: manual, intelligent and motorised. The Ni-U offers high intensity 100W illumination with built-in fly eye optics for even illumination and further superior optical performance is ensured through Nikon's CFI Plan Apochromat Lambda series objectives. Transmission and chromatic aberration correction have been improved throughout the wide range of visible to near IR wavelengths (950nm), allowing use of various fluorescent reagents. They provide bright, high-contrast, high S/N (signal-to-noise) ratio, multi-colour



fluorescence images with almost no focus shift when used with any wavelength. Four new nosepieces include an intelligent sextuple DIC nosepiece option.

The Eclipse Ni-U adds to the newly launched Eclipse Ci series to provide the complete clinical microscope range.

For further information contact Nikon Instruments Europe: Tel: +44 (0)208 247 1718 Email: info@nikoninstruments.eu, www.nikoninstruments.com/NiU

"Better than good" customer satisfaction at Fujifilm



Fujifilm is a pioneer in diagnostic imaging and information systems for healthcare, with a range of constantly evolving, clinically proven, products and technologies designed to assist medical professionals perform efficiently and effectively. To ensure customer satisfaction with their products and services, Fujifilm commissioned an independent agency to undertake a confidential market research survey to assess how the marketplace perceived the company's performance.

Responses from 100 participants were analysed, and Fujifilm are delighted to announce that the overall mean score of the combined quantitative data returned a mean average score of Better than Good. Key areas researched included the overall perception of Fujifilm as a company, satisfaction with image quality, system performance and value for money, as well as satisfaction with staff.

In addition, satisfaction levels of user support and the most important factors considered when purchasing products were also incorporated; along with key journals read and trade exhibitions attended.

A synopsis of the research results is available from Fujifilm. For a copy, or for more information, Tel. +44 (0)1234 326780.

Raising awareness of withdrawal from dopamine agonist treatment

Parkinson's UK is campaigning to raise awareness of dopamine agonist withdrawal syndrome (DAWS) amongst healthcare professionals, as part of its campaign on impulsive and compulsive behaviours.

DAWS happens when a person's dopamine agonist (DA) treatment is stopped or reduced. This could be when a person is experiencing impulsive or compulsive behaviours as a side effect and needs to stop or reduce the medication causing the behaviour. Impulsive behaviour is when a person can't resist the temptation to carry out activities that could lead them to harm themselves or others. Compulsive behaviour refers to an overwhelming urge to act in a certain way, often repetitively.

Impulsive or compulsive behaviours affect around 17% of those who take DAs. Those who are diagnosed with Parkinson's under the age of 50 or who have a history of gambling or addictive

behaviours are most at risk of developing impulsive or compulsive behaviours. Symptoms of DAWS can include anxiety, panic attacks, depression, insomnia, irritability and drug cravings. To avoid DAWS, people with Parkinson's need support from their Parkinson's specialist and withdrawal must be done gradually.

Parkinson's UK has an ongoing campaign to raise awareness of impulsive and compulsive behaviours and associated syndromes such as DAWS. The charity wants to make sure those being prescribed DAs are informed that impulsive and compulsive behaviours are a possible side effect, as well as the potential problems that can arise if they need to stop taking them.

Tracey Ward, Parkinson's Disease Nurse Specialist for Suffolk Community Healthcare, said: "Dopamine agonists can be extremely positive in managing the

symptoms of Parkinson's. However, if person experiences impulsive and compulsive behaviours as a side effect of their treatment then it may be necessary for them to be reduced or, in some cases, withdrawn totally. This is where the risk of DAWS occurs.

"Before taking dopamine agonists it is imperative the patient, and if possible their family or carer, are made aware of the potential for these behaviours and their possible side effects of reduction – DAWS. If patients and families know what to expect, they can often manage much better. The key to withdrawing the medication is support from a specialist throughout, with clear guidance and explanations."

For more information, call +44 (0)808 800 0303 or visit parkinsons.org.uk



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Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – 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 (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 – 18 years)** No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously 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 deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy. Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. 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, hypersensitivity (bronchospasm, anaphylaxis or urticaria). 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. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **Product Licence Number** – 10921/0023.

Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation – December 2009.

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to
Teva Pharmaceuticals Ltd on
telephone number: 01296 719768.

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