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ACNR

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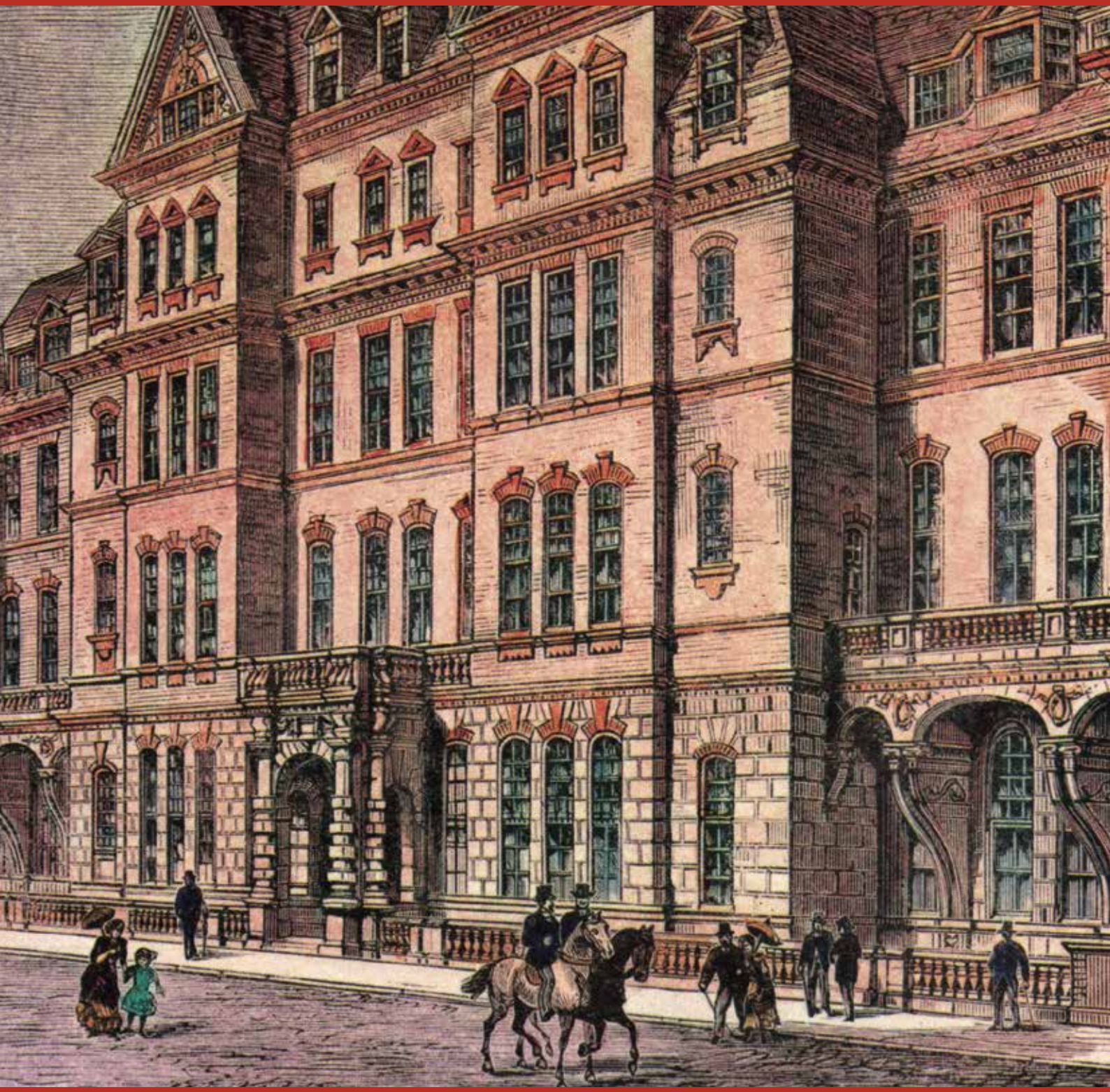
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



BOOK REVIEWS > INDUSTRY NEWS > CONFERENCE PREVIEWS AND REPORTS > EVENTS DIARY

Epilim®

Sodium Valproate

Over the next three months, 100-tablet Epilim presentations will be replaced with 30-tablet packs

This will help ensure that as many patients as possible receive an original pack when Epilim is dispensed, including the new safety warnings and containing the patient information leaflet

Please explain to patients that the pack size is changing to make it more likely that they will receive an original pack with the warnings and the package insert, and encourage them to read this. Reassure them that the medicine has not changed.

Epilim, as effective today as the day it was invented

Prescribing Information: **Epilim®(sodium valproate)** Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentations: ***Epilim 200/500 Gastro-resistant tablets:*** containing 200mg and 500mg sodium valproate, respectively. ***Epilim Crushable tablets:*** containing 100 mg sodium valproate. ***Epilim Chrono 200/300/500 Controlled Release tablets:*** containing a mixture of sodium valproate and valproic acid equivalent to 200mg, 300mg and 500mg sodium valproate respectively. ***Epilim Chronosphere 50mg/100mg/250mg/500mg/750mg/1000mg modified release (MR) granules:*** sachets of microgranules containing a mixture of sodium valproate and valproic acid equivalent to 50mg, 100mg, 250mg, 500mg, 750mg and 1000mg of sodium valproate respectively. ***Epilim Syrup and Epilim Liquid (sugar free):*** both containing 200mg sodium valproate per 5ml. ***Epilim 400mg Powder and Solvent for solution for injection/infusion:*** freeze-dried powder containing 400mg of sodium valproate, with solvent for reconstitution.

Indications: ***All presentations:*** the treatment of generalised, partial and other epilepsy. ***Epilim Powder and Solvent for solution for injection/infusion:*** the treatment of epileptic patients who would normally be maintained on oral sodium valproate, when oral therapy is temporarily not possible.

Dosage and administration: ***Dose Frequency:*** Epilim Chrono and Chronosphere may be given once or twice daily. All other formulations should be given twice daily. ***Adults:*** Dosage should start at 600mg/day increasing by 200mg/day at three-day intervals until seizure control is achieved, usually within the range 1000mg-2000mg, to a maximum dose of 2500mg/day. ***Children over 20kg:*** Dosage should start at 400mg/day (irrespective of weight) with spaced increases until control is achieved, usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored. ***Children under 20kg:*** Dosage 20mg/kg of body weight per day (to the nearest 50mg sachet); in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored. Epilim Chrono should not be used in this group of patients due to the tablet size and need for dose titration. ***Epilim Chronosphere MR Granules*** should be sprinkled on a small amount of soft food or into a drink, which should be cold or at room temperature. Food/drink containing granules should be swallowed immediately; the granules should not be crushed or chewed; the mixture should not be stored for future use. Granules should not be given in babies' bottles as they can block the nipple. ***Epilim Solution for Injection/Infusion:*** Patients already treated with Epilim may continue at their current daily dose using continuous or repeated infusion in normal saline, 5% dextrose or dextrose saline. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800mg (up to 10mg/kg) followed by continuous or repeated infusion up to a maximum of 2500mg/day. Using the solvent provided, the concentration of reconstituted sodium valproate solution is 95mg/ml. Each vial is for single use only, should be reconstituted immediately prior to use and infusion solutions used within 24 hours. Any unused portion should be discarded. Injection or infusion should not be through the same IV line as other IV additives. The solution is suitable for infusion by PVC, polyethylene or glass containers. Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable. Female children and women of childbearing potential Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme. The benefits and risks should be carefully reconsidered at regular treatment reviews. Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses. ***Combination therapy:*** When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. It may be necessary to increase the dose by 5-10mg/kg/day when used with hepatic enzyme-inducing anticonvulsants; the dose may be reduced when these are withdrawn. ***Elderly:*** Dosage should be determined by seizure control. ***Renal impairment:*** clinical monitoring required. Decrease in dosage may be necessary. ***Hepatic impairment:*** Salicylates should not be used concomitantly with Epilim.

Contraindications: In pregnancy unless there is no suitable alternative treatment; in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled. Hypersensitivity to sodium valproate, valproic acid or to any of the excipients listed. Active liver disease; personal, or family history of severe liver dysfunction, hepatic dysfunction, or hepatitis; especially drug related. Patients with urea cycle disorders or porphyria. Patients with known mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), or children under age 2 suspected of having a POLG-related disorder.

Precautions and Warnings: ***Liver dysfunction:*** Severe liver damage, including hepatic failure, sometimes fatal, has been very rarely reported. Most at risk, young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and/or congenital metabolic or degenerative disease associated with mental retardation. Monotherapy is recommended in children under the age of 3 years; potential benefit should be weighed against the risk of liver damage or pancreatitis. Liver function should be measured before therapy and then periodically monitored during the first 6 months of treatment, especially in those who seem most at risk and those with a prior history of liver disease. Epilim should be withdrawn immediately if early symptoms of liver dysfunction develop. In cases of elevated hepatic enzymes (common, particularly at the beginning of therapy), a reduction in dosage may be considered and appropriate and tests should be repeated as necessary. ***Pancreatitis:*** which may be severe and sometimes fatal, has been very rarely reported. If pancreatitis is confirmed Epilim should be discontinued. ***Aggravated convulsions:*** Some patients may experience a reversible worsening of convulsion frequency and severity, or the onset of new types of convulsions when treated with Epilim. Patients should be advised to consult their physician immediately should this occur. ***Suicidal ideation and behaviour:*** has been reported in patients treated with anti-epileptic agents in several indications. Patients should be monitored and advised to watch for signs of suicidal ideation and behaviours, in which case medical care should be sought immediately and appropriate treatment should be considered. ***Carbapenem agents (e.g. panipenem, imipenem and meropenem):*** The concomitant use of Epilim and carbapenem agents is not recommended. ***Patients with known or suspected mitochondrial disease:*** Valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the mitochondrial enzyme polymerase γ (POLG) gene. In patients with a family history or suggestive symptoms, POLG mutation testing should be performed. ***Haematological tests:*** Blood cell count, bleeding time and coagulation tests are recommended prior to initiation of therapy or before surgery, and in the case of spontaneous bruising or bleeding. ***Renal impairment:*** See "Dosing and Administration" above. ***Systemic lupus erythematosus (SLE):*** The potential benefit should be weighed against potential risk in patients with SLE. ***Urea cycle disorders:*** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia. ***Diabetic patients:*** Epilim treatment may lead to false positives in urinary ketone testing. ***Carnitine palmitoyltransferase (CPT) type II deficiency:*** Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Epilim. ***Alcohol:*** intake is not recommended during treatment with Epilim. ***Weight gain:*** Epilim very commonly causes weight gain which may be marked and progressive. ***Lactation:*** Valproate is excreted in human milk and haematological disorders have occurred in breastfed infants of treated women. The decision to abstain from Epilim or stop breastfeeding must balance the benefits of treatment for the mother and breastfeeding for the child.

Female children, women of childbearing potential and pregnant women: *Pregnancy Prevention Programme (PPP):* Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders. The prescriber must ensure that conditions of PPP are followed before prescribing. An Annual Risk Acknowledgement Form needs to be completed at the time of treatment initiation and during each annual review of valproate treatment by the specialist. Please see the SmPC for more details. These conditions also concern women who are not currently

prevent
valproate pregnancy
prevention programme

IMPORTANT NEW SAFETY INFORMATION

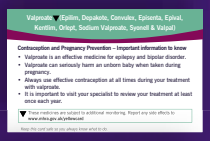
Epilim should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Epilim is contraindicated in pregnancy unless there is no suitable alternative treatment.

Epilim is contraindicated in women of childbearing potential unless the conditions of prevent, the valproate pregnancy prevention programme, are fulfilled.

Information about valproate use can also be found online at www.medicines.org.uk. Enter "valproate" in the search box and then click on "Risk Materials".

Alternatively, please contact your Sanofi hospital specialist or Sanofi medical information department on 0845 372 7101 or email UK-Medicalinformation@sanofi.com.


Valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell & Valpal)

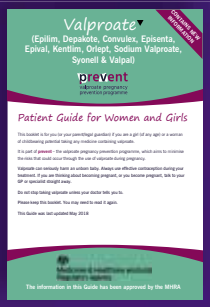
Contraception and Pregnancy Prevention – important information to know

- Valproate is an effective medicine for epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn baby when taken during pregnancy.
- Always use effective contraception at all times during your treatment with valproate.
- It is important to visit your specialist to review your treatment at least once each year.

These medicines are subject to additional monitoring. Report any side effects to www.mhra.gov.uk/yellowcard

Keep this card as you always know what it is for.

A Patient Card is available for the pharmacist to provide to all female patients when dispensing valproate to them



Please provide a copy of the Patient Guide to the patient (or parent/caregiver/responsible person)

SANOFI

sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. *Pregnancy test:* Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy. *Contraception:* Women of childbearing potential (even if she has amenorrhea) who are prescribed valproate must use effective contraception (one user independent method, or two user dependent methods in combination) without interruption during the entire duration of treatment with valproate. *Oestrogen-containing products:* Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy. Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products. Valproate does not reduce efficacy of hormonal contraceptives. *Annual treatment reviews:* The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content. *Pregnancy planning:* If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding planning a pregnancy. *In case of pregnancy:* The patient must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Maternal tonic clonic seizures and status epilepticus carry a particular risk of death for the mother and unborn child; if valproate is used as treatment in pregnancy in the absence of other effective therapies and in acceptance of the known risks, it should be at the lowest effective dose, divided into small doses throughout the day. Use of a prolonged release formulation to avoid high peak plasma concentrations may be preferable. *Female children:* Parents/caregivers of female children who have experienced menarche must be provided with comprehensive information about the risks for children exposed to valproate *in utero*; otherwise, they must understand the need to contact the specialist once the female child using valproate experiences menarche. In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the PPP should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood. *Pharmacists must ensure that:* The Patient Card is provided with every valproate dispensation and that patients understand its content and advise patients not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy. *Educational materials:* The Marketing Authorisation Holder has provided educational materials to reinforce the warnings provide guidance regarding use of valproate in women of childbearing potential and provide details of the PPP. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

Interactions: All combined therapies should be closely monitored, especially at the start of treatment. When appropriate, dosages should be adjusted according to clinical response and blood levels. ***Epilim may potentiate the effect of:*** antipsychotics, MAO inhibitors, antidepressants, benzodiazepines and anti-epileptics with enzyme inducing effect; for example phenytoin, phenobarbital, carbamazepine, primidone, lamotrigine, felbamate, rufinamide, zidovudine, temozolomide, nimodipine, propofol and olanzapine. ***Valproic acid plasma levels may be increased*** in concomitant use with: felbamate, cimetidine, erythromycin or highly protein bound agents (e.g. aspirin). ***Valproic acid plasma levels may be decreased*** in concomitant use with: anti-malarial agents (mefloquine and chloroquine), rifampicin, cholestyramine, carbapenem antibiotics (such as panipenem, imipenem and meropenem), protease inhibitors (such as lopinavir, ritonavir), anti-epileptics (such as phenytoin, phenobarbital or carbamazepine and oestrogen-containing products, including oestrogen-containing hormonal contraceptives. ***Topiramate or acetazolamide:*** Concomitant administration of either, with valproate, has been associated with encephalopathy and/or hyperammonaemia. Co-administration of Epilim and ***Quetiapine*** may increase the risk of neutropenia or leucopenia. Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established. ***Storage:*** Epilim is hygroscopic - keep tablets in blister pack until use and avoid cutting blister strips. Epilim Liquid should not be diluted.

Adverse Reactions: Teratogenicity and developmental effects: 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. Data have also shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. Studies in preschool children exposed to valproate *in utero* show 30-40% experience delays in early development and later, lower intellectual ability and memory problems. Intelligence quotient measured in school aged children exposed *in utero* was on average 7-10 points lower than children exposed to other anti-epileptics. Long term data on outcomes are limited. Children exposed *in utero* are at increased risk of autistic spectrum disorder (approx. three-fold) and childhood autism (approx. five-fold). Limited data suggest that children exposed *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder. ***Very common (≥ 1/10):*** nausea, tremor. ***Common (≥ 1/100 to ≤ 1/10):*** liver injury, severe liver damage, including hepatic failure. Increased liver enzymes (particularly early in treatment, and may be transient). Vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea (frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment). Extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness (for intravenous injection, dizziness may occur within a few minutes and it usually resolves spontaneously within a few minutes), confusional state, hallucinations, aggression, agitation, disturbance in attention, hyponatraemia, weight increase, anaemia, thrombocytopenia, cutaneous hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders, dysmenorrhea, haemorrhage, deafness (a cause and effect relationship has not been established), urinary incontinence. Please refer to the SmPC for full information on adverse reactions. **UK List prices and Marketing Authorisation Numbers:** ***Epilim 200 Gastro-resistant*** 04425/0302: (100 tablets) £7.70, (30 pack) £2.31; ***Epilim 500 Gastro-resistant*** 04425/0303: (100 tablets) £19.25, (30 tablets) £5.78; ***Epilim 100mg Crushable Tablets*** 04425/0317: (100 tablets) £5.60, (30 tablets) £1.68; ***Epilim Syrup 200mg/5ml*** 04425/0301: (300ml) £9.33; ***Epilim Liquid 200mg/5ml*** 11723/0024: (300ml) £7.78; ***Epilim Chrono CR 200mg*** 04425/0307: (100 tablets) £11.65, (30 tablets) £3.50; ***Epilim Chrono CR 300mg*** 04425/0308: (100 tablets) £17.47, (30 tablets) £5.24; ***Epilim Chrono CR 500mg*** 04425/0309: (100 tablets) £29.10, (30 tablets) £8.73; ***Epilim Chronosphere MR 50mg*** 04425/0310: (30 sachets) £30.00; ***Epilim Chronosphere MR 100mg*** 04425/0312: (30 sachets) £30.00; ***Epilim Chronosphere MR 250mg*** 04425/0313: (30 sachets) £30.00; ***Epilim Chronosphere MR 500mg*** 04425/0314: (30 sachets) £30.00; ***Epilim Chronosphere MR 750mg*** 04425/0315: (30 sachets) £30.00; ***Epilim Chronosphere MR 1000mg*** 04425/0316: (30 sachets) £30.00; ***Epilim Powder and Solvent for solution for injection/infusion 400mg*** 11723/0022: (1 vial) £13.32. **Legal Category:** POM. **Marketing Authorisation Holder:** Sanofi, One Onslow Street, Guildford, Surrey, GU1 4SY, UK. **Further information is available from:** Sanofi, One Onslow Street, Guildford, Surrey, GU1 4SY, UK. **Date of Preparation:** December 2018

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Sanofi Tel: 0800 0902314.
Alternatively, send via email to UK-drugsafety@sanofi.com

Ann Donnelly Co-Editor.

Dear readers,

Here is our first issue of 2019. In 'interesting' times, people find comfort in certainty, and simplicity. This journal is a joyous exploration of neurology, written by contributors who have dedicated their careers to finding certainty in an uncertain world.

We explore neurology from myriad angles, ranging from a view into the future of translational research to the individual, unique view of a patient with migraine. A review, published online (https://bit.ly/2Yks5VZ) from Kirsten Revell, of animal models of Huntingtin mRNA suppression and murine models of Huntington's disease, considers how knowledge gained here may potentially lead to benefits in our managment of human disease. Dr Francesca Ammoscato and Dr Sharmilee Gnanapavan summarise current knowledge in biomarkers of multiple sclerosis.

The fixed dilated pupil, in a patient with raised intracranial pressure, is a warning sign to all. How we, as a profession, have come to recognise its significance, and the probable aetiology, is beautifully laid out by Emeritus Neurologist JMS Pearce. He has delineated the historical evolution of our understanding of this sign in a thought-provoking piece.

At the bedside, Dr Sarah Leeder illuminates the requirement for, and process of, screening for pituitary dysfunction in patients with traumatic brain injury. A risk benefit analysis of the use of 'Z' drugs in patients with insomnia, Dr David O'Regan offers us an opportunity to refine our practice and offer our individual patients the best option for them.

We have also reviewed many exciting meetings, including the Encephalitis Society Conference 2018, and David Marsden Movement Disorders Symposium.

In this time of flux one certainty we can share will be that the upcoming ABN meeting, will be a great chance to meet, to exchange ideas and to consolidate our knowledge (and surely test it at the no doubt entertaining and intriguing CPC). Dr Peter Fernandes and Dr Samuel Shribman add to the building excitement by providing us with an overview of the programme, and an introduction to the city of Edinburgh.

We hope you enjoy this issue of ACNR.

Follow us on Twitter & Facebook for latest course, conference and other news: @ACNRJournal
Sign up for our email newsletter, with links to all our content: subscribe at https://bit.ly/2enoO46

Ann Donnelly, Co-Editor
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Alastair Wilkins PhD, is our Case Report Co-ordinator and is Reader in Neurology, University of Bristol and Consultant Neurologist at Frenchay Hospital, Bristol. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

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Angelika Zarkali MBBS (Hons), MRCP, is the Editor of our Conference News section. She is a Specialist Registrar in Neurology in Kent Surrey and Sussex Deanery and has an interest in neurodegeneration and cognitive disorders.

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FEBRUARY-APRIL 2019

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REGULARS

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£2.1m funding received for research into rare childhood disease

Professor Dimitri Kullmann, Professor of Neurology at UCL, Queen Square has received £190,404 from Great Ormond Street Hospital Children's Charity and Sparks, the children's medical research charity, to fund research into the advancement of treatment into epilepsy. This is part of a £2.1 million investment into child health research projects across the UK led by the two charities. This injection of funds in to paediatric research will provide a huge boost to an area of research that is severely underfunded.

Professor Dimitri Kullman is developing a new technique to correct the genetic mistake responsible for focal cortical dysplasia (FCD), the most common cause of drug-resistant epilepsy in children. The treatment aims to stop a child's seizures, which in many cases cannot currently be helped by drugs or surgery. The £2.1 million will support 12 pioneering projects researching some of the most difficult and hard to treat childhood diseases.

For more information visit: www.ucl.ac.uk

New Head of UCL Queen Square Institute of Neurology

Professor Ley Sander, Medical Director at Epilepsy Society, has been appointed as Head of the Department of Clinical and Experimental Epilepsy at UCL Queen Square Institute of Neurology. The comprehensive epilepsy department is ranked number one in the world and spans basic science through to clinical trials. Professor Sander will provide leadership to the department alongside his continuing work with Epilepsy Society.

More information can be found at: www.epilepsysociety.org.uk

2019 WFNR Franz Gerstenbrand Award open for entries

Does your work in neurorehabilitation demonstrate a difference to patient outcomes? If the answer is yes then why not apply for the 2019/2020 World Federation for NeuroRehabilitation (WFNR) Franz Gerstenbrand Award? Worth £3000 to the winner, the Award honours the eminent neurologist Professor Franz Gerstenbrand (1924-2017), and recognises and rewards a neurorehabilitation project that has benefited patients.

Entries for the WFNR Franz Gerstenbrand Award are welcome from clinicians, researchers and allied health professionals who are currently working in neurorehabilitation. Your entry can involve any aspect of neurorehabilitation e.g., a patient or clinic management initiative, research project, best practice development or use of a new technology. The work described must be completed, and produced results, or been published in the last 12 months. The Award is open to all health professionals working in neurorehabilitation but young professionals under 30 years are especially encouraged to enter.

The Award is open to WFNR members and non-members worldwide. The single prize will be awarded as either a travel bursary to a clinical conference, professional development course or research project. The deadline for entries is the 29 November 2019.

For more information and an application form visit:
http://wfnr.co.uk/education-and-research/wfnr-award/

The Children's Trust celebrates top Ofsted rating

The Children's Trust
For children with brain injury

Staff, children and families at The Children's Trust, which helps children and young people with brain injury and neurodisability, were celebrating this week after achieving an 'Outstanding' rating from Ofsted.

The charity, which supported 168 children at its centre last year, received 'Outstanding' in all three areas inspected by Ofsted under the social care framework on 12 December 2018. This news follows a recent Outstanding rating by the Care Quality Commission and ISO9001 accreditation that the charity also received last year.

The Children's Trust residential houses provide placements for children attending the specialist school on site, and the brain injury rehabilitation services.

For more information visit: www.thechildrenstrust.org.uk

Traumatic brain injury and hypopituitarism

Sarah Leeder,
BSc MBBS (Hons) MRCP MRCGP is a Senior Medical Officer at The Townsville Hospital, Queensland, Australia. She graduated from St Georges Hospital Medical School with a first-class degree and with distinction. She is dual trained in both general medicine and general practice and maintains an interest in complex medical comorbidity. Sarah is also involved in leadership and commissioning having completed a Postgraduate Certificate at the University of Brighton with distinction, her work focused on patient engagement and person-centred care.

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Conflict of interest statement:
None declared.

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Summary

- Traumatic brain injury (TBI) is common and associated with significant health and social care costs
- Post traumatic hypopituitarism (PTHP) occurs in approximately a quarter of all patients with TBI and may be a transient phenomenon
- New guidance published in 2017 recommend that all persons admitted to hospital for more than forty-eight hours with TBI should have a pituitary screen three to six months following injury
- All patients admitted with TBI should be screened if symptomatic in any phase post injury
- Limited patient education and resources, problems with the primary and secondary care interface and the challenges of providing integrated care may impact access to screening for PTHP.

Abstract

Evidence demonstrates that the prevalence of hypopituitarism after traumatic brain injury (TBI) is higher than previously anticipated and leads to significant morbidity. Given the prevalence of TBI, there may be a significant pool of patients with undiagnosed hypopituitarism. This places an emphasis on screening to detect the disease and treat it accordingly, as highlighted in guidance published in 2017. The review discusses hypopituitarism following TBI and analyses the potential impact of limited patient education and resources and how current working practice may impact on screening.

Introduction

The incidence of traumatic brain injury (TBI) is variable worldwide. This is most likely due to population based characteristics, fluctuations in methodological reporting and inclusion criteria but it is likely to be within the region of 200 to 235/100 000 per year based on systematic reviews of European and North American populations.[1,2] In England and Wales, approximately 1.4 million patients per year attend hospital following head injury and it is the most common cause of death under the age of 40 years.[3] The sequela of TBI is wide ranging and includes long-term physical, cognitive, and psychological impairments with associated disability.[5] Furthermore, TBI is associated with a significant health and social care cost.[6,7] Due to its impact on society it is imperative that morbidity associated with TBI is recognised and treated to reduce the burden of this common and often life changing condition.[5]

In recent years, there has been an increasing emphasis on hypopituitarism complicating the presentation of TBI.[8,9] It is noteworthy that there is marked disparity in reporting the incidence of post-traumatic hypopituitarism (PTHP). This is, again, due to methodological variance, the use of different screening methods including static and dynamic tests and alternating interpretations of results.[10] This means that the true prevalence is difficult to determine, however systematic reviews and meta-analyses have purported the figure to be in the region of 26% to 28%.[10,11] Furthermore, PTHP can present years after injury underscoring the importance of effective screening.[12] In 2017, the British Neurotrauma Group introduced welcome guidance regarding screening for PTHP in persons with TBI.[13]

Classification:

The classification of PTHP can be described in accordance with anatomical definitions and in time. Firstly, anterior and posterior pituitary dysfunction has been depicted. Secondly, the temporal relationship to the initial TBI has been described.[13] Presentations of PTHP can occur in the acute setting, which is most commonly considered as less than one month (but usually within seven days) after injury. The chronic phase represents the time period after four weeks.[13] Isolated hormone insufficiencies are more prevalent than multiple co-existing endocrinopathies.[14]

Considering anterior pituitary dysfunction somatotropin and gonadotropin deficiencies are most common, followed by corticotropin and thyrotropin deficiency. The potentially life threatening nature of inadequate corticotrophins and impending adrenal insufficiency highlight the clinical relevance of screening. However, it is not only acute life threatening complications that impact on function and quality of life.[14,15]

With respect to posterior dysfunction, the presentation of diabetes insipidus is most common, often transient and can be challenging to diagnose. Again, there is wide variability in the reported prevalence reflecting variations in screening and the difficulties of establishing a diagnosis in the acute phase.[16,17] However, the presentation is associated with other pituitary deficits[16,18] and diagnosis in the early recovery phase post TBI may alert clinicians to be mindful of symptomatology consistent with anterior pituitary dysfunction presenting at a later stage in recovery.

Symptoms, appropriate investigations and treatments are outlined in Table 1 and Table 2.[20]

Risk factors

Numerous factors are implicated as risk factors for PTHP. These include the severity of the brain injury according to the Glasgow Coma Score

Table 1 - Anterior Pituitary Deficiency

Hormone Deficient	Symptoms	Test	Treatment
Growth Hormone (GH)	• Altered body composition o Increased abdominal adiposity o Reduced skeletal muscle mass • Reduced bone mineral density • Fatigue • Dry, thin skin • Psychological features including o depression o anxiety o emotional ability • Raised plasma cholesterol, low HDL • Decreased quality of life	• Insulin like growth factor as screen • Insulin tolerance test	Recombinant Human Growth Hormone – daily subcutaneous injection
Lutenising + follicular stimulating hormone (LH/FSH) in women	• Amenorrhea • Oligomenorrhea • Infertility • Loss of libido • Dyspareunia (short term) • Osteoporosis, premature atherosclerosis (long term)	• Gonadotropin levels – consider menstrual cycle • Oestrogen + progesterone – consider menstrual cycle • Sex hormone binding globulin	Oestrogen Progesterone – topical or oral medication
Lutenising + follicular stimulating hormone (LH/FSH) in men	• Loss of libido • Impaired sexual function • Decreased muscle and bone mass • Erythropoiesis and hair growth	• Gonadotropin levels • Total testosterone • Sex hormone binding globulin	Testosterone – oral medication, intramuscular + subcutaneous injection
Adrenocorticotropic hormone (ATCH)	Acute • Fatigue • Weakness • Dizziness • Hypotension • Nausea + vomiting • Hypoglycaemia Chronic • Tiredness • Pallor • Anorexia • Weight loss • Hypoglycaemia	• 0900 cortisol • ATCH stimulation test	Hydrocortisone + fludrocortisone – oral medication
Thyroid stimulation hormone (TSH)	• Tiredness • Cold intolerance • Constipation • Weight gain • Hair loss • Dry skin • Bradycardia • Hoarseness • Decreased cognition	• TSH • Tri-iodothyronine + thyroxine levels	Thyroxine – oral medication
Prolactin	• Inability to lactate	• Prolactin levels	Unavailable

Table 2 - Posterior pituitary deficiency

Hormone Deficient	Symptoms	Test	Treatment
Anti-diuretic hormone (ADH)	• Polyuria • Polydipsia • Nocturia	• Plasma sodium • Serum and urine sodium + plasma osmolaties • Urine output more than three litres per twenty four hours • Water deprivation test • ADH level	Desmopressin oral or intranasally

(GCS),[20] the mechanism of injury and associated findings on cerebral imaging, pathological changes such as raised intracranial pressure and patient demographics including age and comorbidities. However, the results of analyses of these factors are variable and the evidence is inconclusive. This impacts on identifying appropriate populations to screen and research. It is noteworthy that the numbers included in studies of such populations is relatively small compared to the number of patients sustaining TBI, compounding the difficulties in interpreting results and risk factors.[1-7]

British Neurotrauma Group Guidance (BNGG) 2017

The BNGG provides a comprehensive review of this important topic and the recommendations seek a uniform approach to practice. Algorithms for screening in the acute and chronic phase are clear and concise.

In summary, all persons admitted to hospital with TBI, whose admission time is greater than forty eight hours should be screened for pituitary dysfunction at three to six months post injury.[13] Blood tests including thyroid function tests (TFTs), 0900 cortisol, urea, creatinine, electrolytes, luteinizing hormone and follicular stimulating hormone, testosterone, sex hormone binding globulin and oestrodiol

as age/sex appropriate should be performed. Due to the challenges of growth hormone testing, a referral to the Endocrinology team is proposed to assist in the diagnosis of growth hormone deficiency.[13] Any person, regardless of their presenting history of TBI should be screened in the acute and chronic phase if they are symptomatic[13] (see Table 1 and Table 2 for common symptoms).

Discussion in the context of current literature

It is clear from the BNGG guidance that persons appropriate for screening will present and have their care coordinated by numerous departments and specialty teams.[21,22] Thus, screening will require co-ordination and appropriate communication in primary and secondary care settings. It can be anticipated that the known concerns[23,24] regarding this interface will impact on screening uptake. It follows that the drive for appropriate screening in this population will need to be multi-faceted. The logistical challenge of screening all eligible patients is significant; while BNGG is targeted primarily at neurosurgeons it is relevant to all clinicians and allied heath professionals managing persons with TBI.[13]

International health literature highlights the importance of integrated care to deliver excellent health outcomes including in screening for and preventing disease.[25,26] Here it is noteworthy that the BNGG guidance targets clinicians only. Despite this, it is plausible to argue that an integrated approach, involving allied health professionals and patients and their families/ carers, will be vital in achieving screening to diagnose PTHP.

Beyond the scope of the BNGG but arguably equally important is considering education regarding pituitary screening with respect to the patient and/or their family and carers. Recent literature has highlighted the importance of patient centred care.[27,28] It could be presented that guidance aimed only at doctors' counters this important agenda. In addition, if patients and families are educated and activated as to the importance of screening then they have the potential to drive screening uptake and the diagnosis of PTHP.[29-32] Of note, in commonly searched web based resources containing information designed for patients and families experiencing TBI advice regarding the possibility of PTHP is limited. Synapse[33] and The Brain Injury Association of America[34] contain very finite information regarding endocrine disorders post traumatic brain injury. Only the UK based Headway website[35] dedicates a whole page to PTHP. However, other sources such as the Brain Trauma Foundation[36] and Brain injury Australia[37] had no identifiable resources after searching the terms such as 'endocrine', 'pituitary' and 'hormones'. In addition, only the information available on the Headway[35] website referenced discussing any symptoms with a medical practitioner and stated the possibility of testing. This emphasises the importance of developing appropriate literature and resources with patients and families in mind to empower them to request screening should they experience symptoms associated with PTHP.

It is also important to consider the service implications of screening. Referrals to Endocrinology services may increase affecting overall service capacity. The BNGG recommends that Endocrinology departments should guide investigations for the diagnosis of growth hormone deficiency. This is especially pertinent when considering the presentation of growth hormone deficiency which includes fatigue and psychological disorders. Both of these are very common sequelae of TBI.[38-41]

Given that most common hormone deficits post TBI relate to sex and growth hormones it is prudent to examine the impact of these deficiencies on patients and consider whether a patient will meet the criteria for treatment when contemplating screening. Concerning growth hormone, which has previously been identified as improving outcomes with respect to quality of life and cognition post TBI,[42-44] patients may not be eligible for treatment depending on Clinical Commissioning Group (CCG) uptake of NICE guidance.[45]

Sexual dysfunction following traumatic brain injury is common. However, research pertaining to the medical management of this condition tends to focus on male sexual dysfunction rather than issues related to female gender. With respect to pituitary deficiency testosterone replacement should be considered,[46] but akin to the situation with growth hormone access to testosterone treatment depends on eligibility.[47] Thus screening may highlight deficiencies that clinicians have a limited capacity to treat.

Conclusion

The BNGG have provided commendable and welcome guidance regarding PTHP, however the practicalities of implementing screening have yet to be realised. The BNGG highlights, beyond doubt, the importance of PTHP and its detection in the recovery phase post TBI. It is now the responsibility of everyone involved in the management of TBI to implement the guidance to diagnose and manage this important condition.

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Movement disorders

At first sight, this yellow handbook brings to mind the "Gialli" (Italian for yellow) of Italian bedtime reading; these are the yellow-bound Italian crime novels. And so, Walsh and colleagues set us the task of solving several mysteries in their book, by asking: "What do you do now?".

Thankfully, murder is not usually the answer.

In clinical story after story (31 chapters in total), we explore all types of movement disorders, from the most familiar Parkinson's Disease to all that is unfamiliar, to a medical student at least.

Each chapter begins with a brief case-history; then, having caught the reader's attention, an explanation is provided of what we know so far about the syndrome and its pathology, using tables and brief summaries to aid memory.

All the information is up to date, and this includes news on therapeutic innovations and basic science research (genetics etc.) Throughout, an evidence-based approach is employed, with references provided, allowing for further reading if so wished.

Looking back one sees that the book contains a line of logic, so that individual cases are presented in a kind of sequence. However, the sequence does not obtrude: the writing gets you from one story to the next with very little effort, almost like a soap opera of movement disorders. The style is easy and chatty, without jarring. Medical terms are used and the scientific approach is assured despite the conversational style.

The only flaw in an otherwise excellent book is the lack of indicative titles in the summary.

By contrast, the titles are rather cryptic. While I appreciated the idea of not having the pathology revealed too early when reading through, it would be really useful to have some clear subtitles showing the name of the pathology in the index, in order to facilitate subsequent consultation.

Another observation I made about the structure of the chapters is that the final paragraph "approach to this case" is not always present. I found this paragraph extremely useful. When absent, I sometimes worried that I'd missed the boat.

Assuming that no book has the power to replace the real-life experience, I must admit that this came pretty close. The stories that introduce every chapter have the ability to attract the curiosity of the reader.

For the very interested student, a general Neurologist, a trainee in movement disorders, or a general physician, it is certainly worth reading. I would recommend this book to any professional involved in caring for patients with movement disorders, and the clear language used makes it a rewarding read for students with no prior familiarity.

So thanks to the authors, for explaining difficult concepts in simple terms, and thanks to those who decided on the colour yellow, reminding me that Medicine in general and the subject of Movement Disorders in particular is an extraordinary world, full of mysteries to be solved.

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The misprescribing of Z-drugs for insomnia

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Abstract
Since their development in the 1990s, Z-drugs (e.g. Zopiclone and Zolpidem) have been used in the management of insomnia. Whilst they are widely recognised as being effective, they are not without potential harms. Using evidence-based and common practice approaches, this article discusses the factors which should be considered when prescribing Z-drugs.

Lies are like sleeping pills. You should only use them when you absolutely have to. They spoil everything if you make a habit of them.
Daniel Quinn

Introduction

Scarcely a day goes by without sleep being in the news. One long-running strand concerns media coverage of sleep medicines, particularly the Z-drugs (i.e. Zopiclone and Zolpidem), which have tended over time to receive a bad press. Rising prescription numbers, escalating costs to the NHS, and raised mortality risks all hint at an epidemic of "misprescribing", creating new anxieties for our patients with insomnia to keep them awake at night.

Conversely though, there is a paucity of information available on what constitutes "good" Z-drug prescribing. What is more, various guidelines tend to imply that the right answer exists, rather than recognising the complex trade-offs that often have to be made. One model of good prescribing brings together the traditional balance of benefits and risks, with the need to reduce costs, and the right of patients to make treatment choices[1] (see Figure 1). Using this model, I explore how to avoid misprescribing Z-drugs.

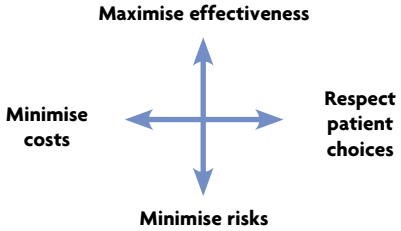

Figure 1 "Good prescribing" - the four aims are shown as a diagram, plotting their commonest conflicts, which may be used to aid discussion and decision making.

Maximising effectiveness

Z-drugs are licensed for the treatment of insomnia, and so the first step in maximising effectiveness is to ensure that one's sleep diagnosis is correct! Choosing between Zopiclone and Zolpidem will then largely be dependent on which period of the night one wants to cover (see Table 1).

Hypnotics are not general anaesthetics, and work best when the sleep-wake cycle is optimised. The best way to achieve this is via Cognitive Behavioural Therapy for Insomnia (CBT-I). Therefore, whenever one reaches for the prescription pad, CBT-I should also be discussed and commenced. CBT-I includes a combination of behavioural and cognitive techniques in order to change maladaptive sleep habits, to lower sleep-disrupting arousal (cognitive or physiological) and to alter sleep-related misconceptions and thought patterns. Whilst it seems logical to advise good sleep hygiene for patients with insomnia, there is no evidence that this is a successful intervention on its own.[2] Access to CBT-I has been cited as a difficulty,[3] but there are a variety of evidenced bibliotherapy and on-line resources which help to circumnavigate this[4,5] (Table 2).

CBT-I shows longer-term benefits than pharmacotherapy,[6] has few physical side-effects (fatigue can be troublesome in the initial stages of therapy), and is preferred by patients.[7] The American Academy of Sleep Medicine's task-force report concluded that CBT-I in uncomplicated cases is associated with an improvement in 70% of patients, and is maintained for at least six months post-treatment.[8] Table 3 compares the efficacy of CBT-I to the Z-drugs in changing sleep parameters. Combination therapy using Zolpidem with CBT-I was better than either treatment alone in one randomised controlled trial.[9] Z-drugs are licensed for short-term use in the UK (i.e. up to four weeks), and are probably ideally used as a stepping-stone until a patient can access or has completed CBT-I. Up to 85% of patients are able to successfully stop their hypnotics following CBT-I, as opposed to 14-28% who are advised by their clinician to do so.[10,11]

Minimising risks

Various adverse events resulting from, or associated with Z-drug use have been extensively reported. Among these, motor vehicle accidents, falls in older adults, and the risk of dementia have attracted the most attention.

A pooled analysis of four studies on Zopiclone's potential for residual sedation contributing to driving risk demonstrated that impairment lasted up to 11 hours post-dosing, and was not dependent on age or sex.[14] Studies on Zolpidem in healthy adults, did not demonstrate any driving impairment with early or middle of the night dosing e.g. (ref 15). However, for adults aged 55-65, deviations in alertness and speed have

Table 1: Comparison of Zolpidem and Zopiclone					
Drug	**Dose range**	**Onset of Action (min)**	**Half Life (hrs)**	**Insomnia Indication**	**Specific side-effects**
Zolpidem	5-10mg	30	1.5-2.5	Sleep Initiation	
Zopiclone	3.75-7.5mg	30	5-6	Sleep Initiation, Maintenance	A metallic taste side-effect occurs in up to 40% of patients

Table 2: Accessing CBT-I	
CBT-I Formats	**Comment**
Bibliotherapy	e.g.: 1. Overcoming insomnia and sleep problems: A Self-Help Guide Using Cognitive Behavioral Techniques by Colin Espie 2. How to Beat Insomnia and Sleep Problems One Step at a Time: Using evidence-based low-intensity CBT by Kirstie Anderson (both available from community libraries)
Online	e.g.: 1. Sleepstation – https://sleepstation.org.uk 2. Sleepio – https://www.sleepio.com
Increasing access to psychological therapies (IAPT)	Many IAPT services now offer CBT-I to which patients can self refer. https://www.nhs.uk/service-search/Psychological-therapies-(IAPT)/LocationSearch/10008

Table 3: Comparison of CBT-I, Zolpidem and Zopiclone effects on sleep parameters			
Drug	**Change in Sleep Onset Latency (min)**	**Change in Total Sleep Time (min)**	**Change in Sleep Efficiency (%)**
CBT-I	-15.5A ; -33.8B	-14.4A,C ; + 32.7B,C	+6.5A,C ; +14.5B,C
Zolpidem	-6.1A ; -12.8B	-51.6A ; + 69.2B	+2.1A ; +2.1B
Zopiclone	-6.8A	-65.6A ; + 34.6B	-0.8A ; +8.1B
A Measured by polysomnography. *B* Measured by sleep diary. *C*, average data from two clinical trials comparing CBT-I vs Zopiclone and CBT-I vs Zolpidem[12,13] + = increase; - = decrease.			

Table 4: Comparison of costs of Z-drugs versus Temazepam	
Drug	**Cost for 28 days £**
Zolpidem	0.92
Zopiclone	0.92
Temazepam	1.49
Lowest NHS indicative and tariff prices as listed in the British National Formulary online (accessed March 2018).	

been reported.[16] The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) has ranked various medications based on their potential for causing impaired driving (I = presumed safe, II = minor to moderate impairment, III = severe impairment), with Zopiclone ranked at III and Zolpidem ranked at II.[17] Younger drivers, those new to the Z-drugs, sleep deprivation and combination with alcohol and other sedative medications all increase the risk. It is therefore important to warn patients of this potential risk when commencing Z-drugs.

The literature on Z-drug associated falls in older adults has yet to reach a consensus. For every study that demonstrates an association, there is another which refutes it e.g. (ref 18). Moreover, insomnia on its own confers a risk of falls in this age group.[19] The risk is certainly increased, when older adults are prescribed a Z-drug which is ineffective for them. Being awake and mobile in the night with a Z-drug on board will increase the risk of falls. Therefore, if the Z-drug is ineffective, it should be stopped. Higher Z-drug doses, psychotropic poly-pharmacy and poor mobility all increase the risk of falls and subsequent bone fractures.

Dementia of any type remains one of the most feared disease states, and any association with Z-drugs is a common worry for patients with insomnia. For many patients, Z-drugs certainly cause acute and reversible cognitive dysfunction (e.g. amnesia, slurred speech etc). However, whether or not they cause progressive neurodengerative disease has yet to be elucidated. The evidence relating to Z-drugs being associated with dementia is scant, and is mostly dependent on a few sub-analyses of wider benzodiazepine studies e.g. (ref 20). One single Taiwanese case–control study reported an increased risk of dementia with Zolpidem compared with for non-users.[21] However, sleep disturbance is a common early symptom of dementia, and whether these patients were already on a dementing trajectory remains unknown. For now, clear evidence of a drug-induced neuropathological mechanism has not been demonstrated, and the criteria required to substantiate a causal relationship has not been fulfilled.

Z-drugs are associated with NREM Parasomnias (e.g. sleepwalking, sleep driving), with Zolpidem being the most strongly associated.[22] Whilst sleepwalking is generally innocuous, it can result in injury to the sleepwalker and to others.[23,24] The product information for Zolpidem cautions that sleepwalking may occur when Zolpidem is combined with alcohol, other CNS depressants, and when used at doses greater than 10mg (i.e. the maximum recommended dose). It would appear that the incidence of sleepwalking is not dependent on age, sleepwalking history or medical history. However, higher rates are seen in patients taking Zolpidem combined with other psychotropics (e.g. antidepressants and antipsychotics).[22] When prescribing Z-drugs, it is therefore important to warn all patients of the potential risk of NREM Parasomnias, to monitor for them, and to consider an alternate hypnotic if they occur.

The risk of fatality from Z-drug mono-overdose via respiratory or nervous system depression appears non-existent.[25] It is their combination with other suppressants, such as alcohol, opioids and muscle relaxants which increase the risk. As for the other newer safety concerns regarding Z-drugs e.g. risk of cancer, infection, pancreatitis and increased mortality etc, no studies demonstrating causation have been published. As one is innocent until proven guilty, epidemiological association does not equate to causation.

Minimising costs

Insomnia is estimated to cost the US economy $63-90bn a year.[26,27] These costs include direct treatment costs, such as physician encounters and prescriptions, as well as indirect costs, such as consumption of medical services, increased accident risk, and lost workplace productivity. One study suggested the latter is accountable for up to 76% of the economic burden.[28] There are no comparable figures for the UK, though one study estimated insufficient sleep (characterised as sleeping less than six hours per night) as costing the UK $50bn a year.[29] The manufacturers of the Z-drugs submitted economic models to the National Institute for Clinical Excellence (NICE) which concluded that any additional acquisition costs (over and above traditional benzodiazepines) would be reduced by lower consumption of other healthcare resources and/or lead to an improvement in health outcomes as a result of decreased dependence or reduced residual effects.[30] NICE rejected their economic models, based on the "lack of compelling evidence on any clinically useful differences between the Z-drugs and the shorter-acting benzodiazepine hypnotics", and concluded that the lowest cost drug should be used.[30] As Table 4 highlights, their advice

would currently be in favour of the Z-drugs. Despite any arguments made, there is currently a paucity of published economic evidence to support NHS decision making in this area. Economic evaluations alongside randomised clinical trials would need to be conducted in order to build a clinical and economic evidence base to inform decision making.

Respecting patient choice

Despite guidelines advocating the short-term use of Z-drugs, many of us will have patients who require them for longer than the licensed maximum period of four weeks. Sadly, these patients are often made to feel like drug-seeking pariahs.[31] The associated anxiety and guilt they feel from requesting additional prescriptions, often compounds the torture of the night; another perpetuating factor to drive their insomnia.

Insomnia is a real and frequently chronic condition. Its associated adverse quality of life effects (akin to significant depression.[32]), and the risks it poses to mental health, are often minimised by health care professionals.[31] Z-drugs offer one potential treatment solution, and whilst every effort should be made to encourage patients to engage in a non-medication alternative i.e. CBT-I, there will be a proportion for whom this treatment is not desirable, suitable, or effective. Many patients are happy with their Z-drug treatment, and show no signs of drug misuse or of developing tolerance or dependency – in their eyes, if it's not broken why fix it? In 2005, the FDA approved two Z-drugs (Eszopiclone and Zolpidem extended release; both unavailable in the UK) without placing restrictions on their therapeutic timeline. Perhaps as our knowledge of the safety profile of these hypnotics increases, so too will our confidence to question current guidelines.

Despite media scaremongering of a Z-drug epidemic, one UK study showed that 0.69% of 18 to 80 year-olds were taking benzodiazepines and Z-drugs for more than one year.[33] When applied to nationwide patient numbers, the British Medical Association equated this to between 265-295,000 patients using long term benzodiazepines and Z-Drugs.[34] As a comparison, in 2015, it was estimated that 6% of the UK population (which was extrapolated to 950,500 people) had been using over-the-counter painkillers for more than a year.[35]

As with any other medication, once a Z-drug is initiated it should be regularly reviewed, and monitored for signs of emerging misuse, tolerance or dependency. Prescribing higher than the maximum recommended dose of a Z-drug is not advised. If a Z-drug at the maximum dose looses efficacy, then a re-assessment (including for co-morbid sleep, physical and mental health disorders) is warranted. The Z-drug should be withdrawn slowly (as to avoid rebound insomnia), and replaced (if appropriate) with an alternative hypnotic. These alternatives are often low-dose sedative anti-depressants or anxiolytics, where there are parallels in our knowledge deficits regarding their long-term use and safety.[36]

Several authors have suggested that Z-drugs have a lower risk and misuse potential when compared to benzodiazepines.[37,38] It has been postulated that this is because of their lower affinity for the alpha-2 subtype. However, careful consideration should be given before initiating Z- drugs to patients with a past history of alcohol or drug misuse or dependency, as this may increase the risk. In monitoring for potential misuse, using a Z-drug for purposes other than insomnia (e.g. as an anxiolytic), and seeking more before a prescription has expired should raise concern. In relation to the latter, it is advisable that there is only one prescription source, and it is often safer that this is undertaken by the GP, who will have more regular patient contact, as well as a more holistic overview of their health and social difficulties.

Future directions

Rather than scaremongering and media dictates, long-term efficacy, safety, quality of life and economic studies are needed to guide our prescribing of Z-drugs for insomnia. Moreover, these studies should include "special populations", such as the elderly, and those with chronic medical and psychiatric co-morbidities. Such studies will be challenging, but they should be approached with an open mind; lies may not be like sleeping pills.

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Biomarkers in MS – the current state of play

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Abstract
Since the late 80s with the discovery of oligoclonal bands (OCBs) in the CSF of Multiple Sclerosis (MS) patients, scientists have made huge efforts to develop prognostic biomarkers in both the CSF and blood. In general terms, the latter has resulted in the development of either immune system activation/regulation biomarkers, or neurodegenerative biomarkers. Simply put, from a biomarker perspective, disease progression in MS is due not only to the underlying autoimmunity, but neurodegeneration. As there has been resurgence of interest in the OCBs with the 2018 McDonald criteria, we discuss this first in the review.

We then highlight some of the other promising diagnostic and prognostic biomarkers in MS, including osteopontin, microRNAs, neurofilaments, chitinase and chitinase-like proteins.

Introduction
Multiple sclerosis (MS) is a progressive inflammatory demyelinating disease of the central nervous system (CNS). It is now well accepted that Th1 and Th17 cells play an important role in the pathogenesis of MS, but contrary to belief, they are not the only cells involved. A combination of antibody-producing B cells/plasma cells, macrophages, and NK cells are involved in disease pathogenesis, whilst demyelination, inflammation and axonal damage contribute to progressive disability in MS patients. Over the last few years, scientists and clinicians have worked together in order to identify specific biomarkers able to predict the onset and course of the disease. However, despite the dramatic increase in publications, the biomarkers commonly used in clinical practice still remain the cerebrospinal fluid (CSF) oligoclonal bands, and more recently the neurofilament proteins. In this review we summarise the biomarkers that have made waves in MS research over the last ten years, including osteopontin, microRNAs, neurofilaments, chitinase and chitinase-like proteins. We also discuss oligoclonal bands, particularly as these have been reintroduced into the latest diagnostic criteria for MS.

Oligoclonal bands
Immunoglobulin IgG oligoclonal bands (OCB) are detected in about 95% of MS patients and are considered the best diagnostic element supportive of MS diagnosis. Although OCBs are found mainly in CSF of people with MS, they also occur in other inflammatory conditions like paraneoplastic disorders, CNS lupus, neurosarcoidosis, Behcet's disease and various forms of cerebral angiitis. OCB negative MS patients have been reported to have fewer infratentorial and more juxtacortical lesions compared to OCB-positive patients.[1] OCB negativity is also associated with better prognoses based on physical disability.[2]
If we focus on the prognostic significance, Tintore et al. found that those who are OCB positive had a higher risk of conversion from a clinically isolated syndrome (CIS) to clinical definite MS.[3] It therefore adds information to MRI in the first attacks of MS, and henceforth has been re-introduced back into the 2017 McDonald criteria.[4] Several studies have also investigated the correlation between OCBs and cerebral volume. Ferreira et al., studied both grey and white matter volumes, and noted less brain atrophy in those who were OCB negative.[5] While Fenu et al. found that brain atrophy in OCB positive patients primarily involved the white rather than grey matter.[6]

Osteopontin
Osteopontin (OPN) is a pleiotropic cytokine expressed by immune cells, including T cells, dendritic cells, macrophages and natural killer cells.[7] It is involved in a variety of physiological functions and pathological states such as bone remodelling, wound healing, cancer biology and vascular disorders, and exerts pro-inflammatory and pro-angiogenic effects.[8] OPN is considered to be a pro-inflammatory mediator that amplifies the inflammatory process by enhancing the production of interferon gamma (IFN-γ) and IL-17 from T cells with consequent inhibition of IL-10.[9]

Elevated OPN gene expression was found in MS brain lesions compared to control brain tissue[10] and these findings were also confirmed in analysis of spinal cord tissue in experimental autoimmune encephalomyelitis (EAE).[11] Many studies have reported increased concentration of CSF OPN in relapsing remitting MS (RRMS) patients compared to CIS and secondary progressive MS (SPMS) patients. Similarly, plasma OPN levels have been found to be increased in RRMS compared to healthy controls.[12] However, a raised CSF OPN or blood OPN is not specific for MS, and has also been demonstrated in Alzheimer's disease and Parkinson's disease.[13,14]

MicroRNAs
Micro RNAs (miRNA) are short non-coding RNAs with an important role in post-transcriptional gene expression by silencing; via binding of the target messenger (mRNAs) or by degrading the mRNA transcript. MiRNAs play a major role in regulating key processes in immune cells, including Th1, Th17, T-regs,[15] as well as being found in a number of neurological disorders, including traumatic CNS injuries.[16] More recent findings suggest a role for miRNAs as biomarkers in MS.[17] Huang et al. identified a link between dysregulated miRNAs

and MS.[18] Specifically, higher concentrations of miRNAs were observed in the serum of MS patients compared to controls[19] and among these let-7i miRNA has been found to reduce the number of T-reg IFNy-IL17A-Fox3P-CD4+ cells, by targeting insulin like growth factor 1 receptor (IGF1R) and transforming growth factor beta receptor 1 (TGFBR1).[20] The impairment of T Reg cells, with consequent disruption of the immune homeostasis, is considered crucial in the initiation and perpetuation of autoimmune disease.[21]

Neurofilaments

Neurofilaments, an abundant protein in the cytoskeleton neurons are composed of the subunits light (NfL; 60–70 kDa), medium (NfM; 130–170 kDa) and heavy chain (NfH; 180–200 kDa). Although the precise mechanism of axonal loss in MS is still not clear, it has been repeatedly demonstrated that neurofilaments are released into the blood and CSF of MS patients after episodes of relapses and with slow neurodegeneration. They are detectable in most at diagnosis, and even at the early stages of CIS and radiologically isolated syndrome (RIS).

The research has come a long way since MRI was the only tool available able to monitor the course of the MS status and there is the need to explore biomarkers that can accurately be detected at a very early stage of the disease. Among these biomarkers, NfL emerged as a favourable candidate. There are many reports backing its usefulness early on in prognostication, with increased levels predicting the development of MS in CIS and RIS.[22]

In MS, NfL levels in CSF and serum increase with EDSS, whilst the incremental rise correlates with lesion load and worsening EDSS.[23] Following natalizumab use, a treatment effect on NfL levels has been demonstrated in the CSF but not in the serum, indicating a relationship between anti-inflammatory therapy and axonal damage resolution.[24,25] However, with the increased sensitivity of Simoa platform, there has been new exciting research investigating NfL levels in the serum, raising the possibility of a blood biomarker. To date good correlations have been demonstrated between serum NfL and CSF NfL,[26] MRI activity and disability in CIS patients. At a cohort level serum NfL have definite utility in monitoring treatment effect and reduced levels have been documented with interferon beta[27] and fingolimod,[28] and may be a useful surrogate marker of treatment efficacy in clinical trials. At an individual level, it's long-term predictive capacity is uncertain.

NfH, like NfL is a bulk biomarker of neuronal damage and has been found to be elevated in optic neuritis,[29] in RRMS and SPMS and correlates with EDSS in cross sectional and longitudinal studies.[30,31] NfH levels have been demonstrated to improve following lamotrigine treatment in SPMS and phenytoin in optic neuritis; two neuroprotection studies in MS.[32,33] Antibodies to NFL have also been identified in MS, with elevated levels in CIS, primary progressive MS (PPMS) and RRMS and have been linked with clinical disability and progressive disease course. Their significance in MS is as yet not known.

Chitinase and Chitinase-like proteins

Chitinase (chitinase 1, CHIT1) and chitinase-like protein (chitinase 3-like protein 1, CHI3L1 and 2, CHI3L2) are chitin-binding proteins that belong to the glycohydrolase family 18 and may be indicators of inflammation.

Recent evidence indicates CHIT1 gene expression is greater in chronic active MS lesions, infiltrated by microglia and macrophages, compared to expression in the rim of active MS lesions.[34] CHIT1 CSF levels were significantly higher in RRMS compared to controls. Novakova et al. showed a reduction in CSF CHIT1 in fingolimod-treated MS patients switched from first-line DMTs but they did not find a similar trend in natalizumab-treated patients.[35] Hinsinger et al. showed that chitinase-like proteins, CHI3L1 and CHI3L2 are highly expressed in white matter plaques, specifically in astrocytes and microglial cells of MS patients.[36] CHI3L1 has drawn attention in that it has been observed to be increased in CIS cases converting to MS compared to non-converters[37] and the same trend was not confirmed in RIS patients.[38] This observation, together with the evidence that CSF CHI3L1 increase accordingly to the progression of MS may represent an alternative diagnostic value to discriminate progressive patients at a very early stage. Since OCB testing fails to detect intrathecal IgG synthesis in about 5% of MS cases,[39]

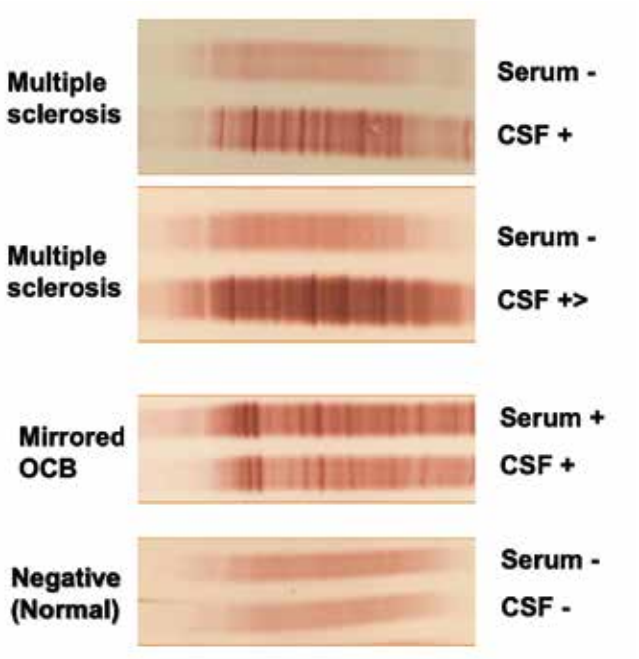

Figure 1: Oligoclonal bands are indicative of intrathecal synthesis of immunoglobulins. It is present in MS (CSF+ Serum-; CSF+ › Serum -) but can also be found in infections, and sometimes in other autoimmune disorders. A mirror OCB pattern (CSF+ = Serum-) is not evidence of intrathecal synthesis but consistent with passive transfer of immunoglobulins from a systemic source.

determination of CSF CHI3L1 levels by ELISA may represent a future alternative to be utilised in MS clinical practice. In addition, reduced CSF CHI3L1 has been observed after 12 months of natalizumab treatment,[40] reflecting the initial observations that this is a biomarker of inflammation. CHI3L1, is not specific for MS and has been found to be elevated in cancer and rheumatoid arthritis.[41]

CHI3L2, on the other hand, was originally thought to be a secretory product of chondrocytes, and as such has only recently been studied in MS. Unlike CHI3L1, CSF CHI3L2 decreased in PPMS compared to RRMS patients.[36] A rise in CHI3L2 observed in RRMS and also correlated with other biomarkers of inflammation and tissue damage such as NfL, OPN and MBP,[42] suggesting like the others an association with inflammatory activity.

Conclusion

In the past, MS was considered to be an exclusively T-cell mediated-disease, but increasingly it is clear that we are dealing with a multifactorial disease pathogenesis leading to progressive disability. Understanding the role of each of these factors may allow for better definition of the underlying predominant disease process in each patient, permitting more individualised therapeutic strategies. The drive to find new validated biomarkers in MS to facilitate this process has often had unpredictable results. We now understand that the majority of these biomarkers are either indicators of bulk tissue injury i.e. neurodegeneration or inflammation, or impaired immune regulation in MS.

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The dilated pupil and brain herniation

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Abstract
This paper recalls the descriptions and early ideas about the dilated pupil accompanying raised intracranial pressure resulting from head injuries and space-occupying lesions. The observation of the ominous fixed, dilated pupils in those with expanding brain lesions dates to Richard Bright and Jonathan Hutchinson in the 19th century, but its significance and mechanisms were only debated in the early years of the 20th century. Compression or stretching of the oculomotor nerve were considered possible causes, but the related mechanisms of coning and the importance of lateral shift were only more recently realised.

FEW investigations of late years have excited more interest than those which have been made into the connection of certain changes in the eye with diseases of the central nervous system, and into the additional means of diagnosis which such changes may afford.
Sir Thomas Clifford Allbutt ,1872.[1]

Not until the early 20th century was the importance of a fixed dilated pupil recognised as an ominous physical sign. It became a neurosurgical axiom that a fixed dilated pupil occurs ipsilateral to a pressure cone caused by a space-occupying lesion with intracranial hypertension.[2]

Brain herniations are traditionally classed as: subfalcial, uncal (transtentorial), and cerebellar tonsillar. They can complicate head injury or any other causes of a brain mass or swelling.[3] Central herniation, usually preceded by uncal and cingulate herniation, is the downward movement of the brain through the tentorial notch. Clinically it is manifested by stupor leading to coma; small, reactive pupils becoming fixed and dilated; with irregular breathing, leading to decerebrate posture, and ultimately death. With herniation, the ipsilateral posterior cerebral artery may be compressed adding to the ischaemia induced by brain oedema.

Observations of raised intracranial pressure, and more recently papilloedema (in early accounts described as 'choked disc', *stauungspapille*, or optic neuritis) were recorded more than a century ago.[1,4] But neither the mechanisms nor clinical significance of the associated dilated pupil were fully understood.

The redoubtable surgeon, Percivall Pott (1714-1788) detailed his *Observations on the Nature and Consequences of those Injuries to which the Head is liable from external Violence*[5] and referred to the woodcuts of the surgeon Hans von Gersdorff (c.1455-c.1529). But Pott failed to mention the ocular signs in von Gersdorff's ancient woodcut, the work of Johannes [syn. Hans] Wechtlin, contained in his *Feldbuch der Wundartzney* (Fieldbook of wound medicine) 1517. This illustrated the elevation of a depressed skull fracture. The patient shows a slightly dilated right pupil and the eye is abducted, suggesting a partial third nerve palsy (Figure 1) It has been said that his observation was not repeated for another 300 years. However, in this oft-cited instance[6] there is insufficient evidence to wholly exclude an unrelated strabismus with a physiological asymmetry of the pupils of up to 0.4 mm, found in about 20% of normal people.

Figure 1. Hans von Gersdorff (surgeon) Fieldbook of wound medicine (1517). Treatment of a skull injury. Wood cut work attributed to Hans Wechtlin. In public domain

John Cheyne (1777-1836), remembered for Cheyne-Stokes respiration, studied medicine at Edinburgh, where Alexander Monro secundus (1733-1817), who described the interventricular foramen, was one of his teachers. In cases of apoplexy, Cheyne believed that cerebral anaemia might be the cause; in an early case in 1812 he recorded the contraction and dilatation of the pupil and noted, 'Thus we do not despair until the pupil ceases to contract.'[7]

Richard Bright
A more comprehensive description is found in 1831, in Volume two* of Richard Bright's (1789-1858) (Figure 2) famous case reports[8] devoted to neuropathology[9] with 54 magnificent plates (Figure 3). William Munk in his Roll was justifiably dazzled by Bright's abilities: 'Dr. Bright showed the most sagacious observation, untiring industry, and wonderful powers of investigating truth, the end and aim of all his work.'[10] Bright reported the ipsilateral dilated pupil in a man whose post-mortem showed an epidural haematoma with petechial haemorrhages in the brain after head

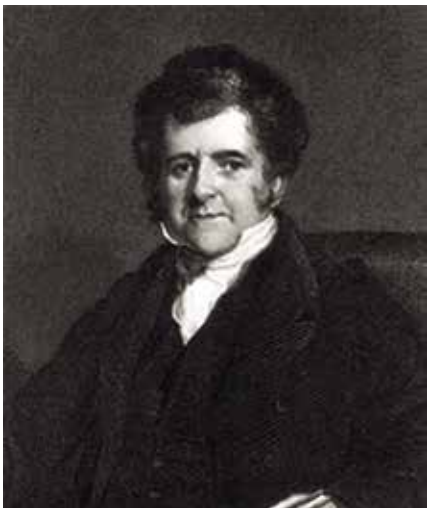

Figure 2. Richard Bright (from http://blueplaquesguy.byethost24.com/images/Bright_Richard_1.jpg)

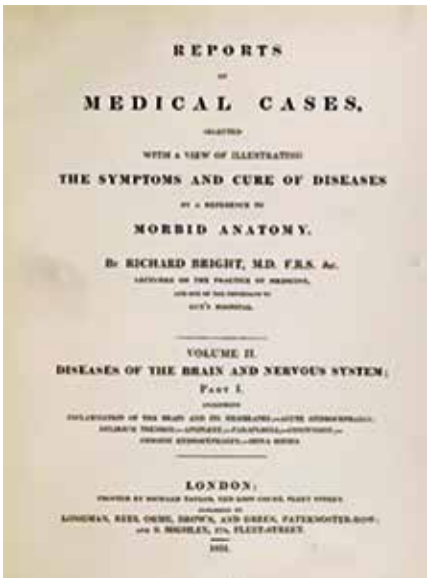
REPORTS
MEDICAL CASES,
THE SYMPTOMS AND CURE OF DISEASES
MORBID ANATOMY.
By RICHARD BRIGHT, M.D. F.R.S. &c.
VOLUME II.
DISEASES OF THE BRAIN AND NERVOUS SYSTEM;
Part I.
LONDON:

Figure 3. Bright's Reports on Medical Cases (Vol 2).

injury (case 191).[8,11] On the second day after a well described lucid interval the patient was noted to be less responsive and to have a slow pulse. Bright observed:

> A 38-year-old man working at a large wharf below London bridge fell from a height of 11 or 12 feet. The following day his language was incoherent and speech scarcely articulate, and he complained of pain in the head. He was bled, and on the third day he is in a state of stupor, but may be roused to answer question. The muscles of the left side of the face are paralyzed... right pupil dilated. He died the sixth day and an autopsy was performed. An epidural hematoma was found. In general the pupils sometimes contracted, at other times dilated, and acting quite irregularly under the stimulus of light.

Bright described another case, a 20-year-old man with apoplexy whose pupils dilated, and did not contract when a candle was brought near. He clearly recognised the importance of this vital clinical sign; however, he suggested no mechanism.

Bright's salient observation may have prompted the experiments of Ernst Viktor von Leyden (1832-1910), which in 1866 showed that with increased intracranial pressure, the pupils first became narrow, then dilated, but not always symmetrical, accompanied by coma with a slow pulse, impaired respiration and death.[12] Five years later, Alexander Pagenstecher (1828-79) studied consecutive reactions of the pupil with increasing experimental pressure, noting an initial constriction followed by a dilated fixed pupil with stupor or coma.[13,14] The controversial Guy's hospital surgeon and anatomist Astley Paston Cooper (1768-1841) also experimented on dogs, manually compressing the exposed dura, trying to distinguish compression from 'simple concussion'. In humans he explained the symptoms caused by compression:[15] (lecture XVII):

> The breathing being stertorous, the pulse slow, and the pupils dilated; ...when you then find a patient with the apoplectic stertor, slow pulse, dilated pupils, it will generally happen that the brain is compressed.

Hutchinson's pupil

It remained for Jonathan Hutchinson (1828-1913)[16] (Figure 4) in 1867 to provide a more detailed report of his experience with human head injuries and his observations of a dilated pupil on the side of a fatal traumatic epidural haematoma:[17]

> …*Unilateral dilatation of pupil after injury to the head.* A man had died in whom this symptom was present, and in whom we found a large clot of blood between the dura mater and the bone pressing forwards upon the sphenoidal fissure, and no doubt compressing the trunk of the third nerve. …We can have little hesitation in assuming that the cause of death was compression of the brain.

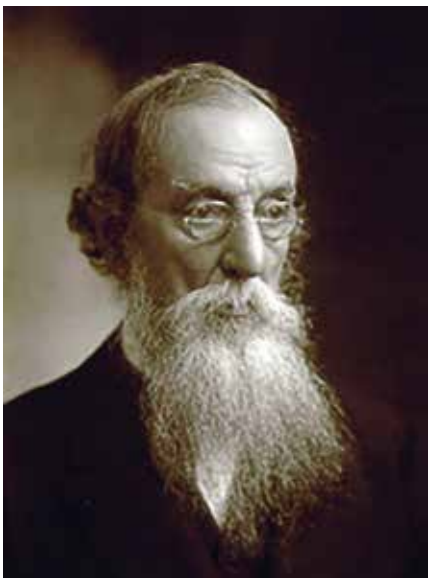

Fig 4. Sir Jonathan Hutchinson (from http://www.odermatol.com/wp-content/uploads/image/2013%201/33%20epo/34aj_%20Sir%20JONATHAN%20HUTCHINSON.jpg

Hutchinson also reported a boy, who was admitted on a Thursday, having been knocked down in the street and possibly run over. He did not relate the dilated pupil to transtentorial shift, but invoked the mechanism of third nerve compression that affects the ocular parasympathetic causing the pupil to dilate, and to fail to constrict in response to light:

> From the position of the clot there can be little doubt that the third nerve is compressed and thus, the dilatation of the pupil is explained. These two cases, so exactly parallel, seem to supply us with a new and very valuable symptom indicative of effusion of blood in this situation. … You will see that beyond the symptoms which usually attend cases of severe concussion of the brain (accompanied as they frequently are by more or less of contusion also), we had had none excepting the dilatation of the right pupil. The boy had been conscious up to within about half an hour of his death; he had had a rapid pulse and great restlessness throughout; he had had no observable paralysis.[17]

The Guy's hospital surgeon, WHA Jacobson (1847-1924) suggested in 1886, that this phenomenon should be named 'Hutchinson pupil'.[18] He may have neglected Bright's earlier account.

William Macewen (1848–1924) in 1887 considered pupillary dilatation to be a sign of oculomotor nerve irritation, paralysis or vascular changes in connection with a middle cranial fossa clot.[19]

Duret Haemorrhage

Henri Duret (1849–1921) a surgeon, who trained with Charcot and Vulpian,[20] reported that blows on the head in animals increased intracranial pressure. He observed loss of consciousness, rigidity, slow then faster breathing, and mid-dilated pupils; days later the pupils constricted and the animal died. In addition to the cerebral damage at autopsy he observed 'haemorrhagic lesions in the superior part of the bulbar base', which proved 'that the blows to the skull may have a considerable effect on the bulbus':[21,22]

> A dotted line of haemorrhages on the floor of the medulla's thickness and around the central canal… this is explained by the fact that at the time of impact, the fluid in the ventricles has an effect on the cerebral aqueduct, the fourth ventricle and, especially, the spine's central canal.

Mistakenly, he considered:

> the sudden cessation or suppression of brain function subsequent to an impact to the skull is produced by means of the cerebrospinal fluid, which transmits the damaging action to regions of the brain capable of generating all the observed phenomena.

This mechanism he termed *choc céphalo-rachidien* (cephalospinal shock). He distinguished two stages, first, pupil constriction by bulbar lesions due to *choc céphalo-rachidien*, secondly, dilatation from the accumulation of blood around the oculomotor nerve. Theodor Kocher (1841–1917), a Swiss surgeon then used the eponym 'Duret haemorrhages' in his comprehensive review of brain injuries.[23]

Later investigations

The German surgeon, Ernst von Bergmann (1836–1907), a keen advocate of Lister's aseptic techniques, described fixed dilated pupils in his text on brain injuries.[24] He observed that the ipsilateral pupil became narrower at first and then, with increased pressure leading to coma, it dilated.

In 1904 James Collier observed both the cerebellar pressure cone and 'false localising signs' in cases of intracranial tumour examined clinically and pathologically.[25] He distinguished this from the dilated pupil of uncal herniation.[26] He commented:[27]

> In many cases of intracranial tumour of long duration, it was found post-mortem that the posterior inferior part of the cerebellum had been pushed down and backwards into the foramen magnum and the medulla itself somewhat caudally displaced, the 2 structures together forming a cone-shaped plug tightly filling up the foramen magnum.

Adolf Meyer (1866-1950) related the pressure on the third nerve to herniation of the uncus into the incisura angularis.[28] Similarly, Sir Geoffrey Jefferson (1886-1961) described in four cases the mechanism of temporal lobe herniation: a pressure cone formed by uncal herniation on the crus cerebri, with resulting impingement on the oculomotor nerve.[3]

Later accounts of Kernohan-Woltman's notch of the crus cerebri causing ipsilateral hemiplegia[29] were followed by the newer concept that depression of alertness corresponded to distortion of the brain by horizontal rather than vertical displacement.

Holman and Scott pointed out that although a dilated pupil was valuable in locating the site of injury, there were only a few descriptions in the literature of patients who deteriorated and lapsed into coma.

> The mechanism of its appearance is not obvious, but it is assumed that the intracranial course of the third nerve, as it lies against the bony wall of the cranium, lends itself peculiarly well to compression from a pressure applied lateral and superior to it.[30]

This mirrored Hutchinson's cautionary comment:

> This case adds another to a considerable series which we have recently had showing that the orthodox symptoms of compression of the brain, absolute insensibility, stertor, slow, laboured pulse, and hot surface, are not by any means always met with…[17]

Holman and Scott echoed Horsley's earlier report[4] of the consequences of this sign for surgery:

> '[We] place reliance on the unilateral dilatation and fixation of the pupil as an indication of unilateral cerebral compression, due more particularly to haemorrhage…Unilateral dilatation and fixation of the pupil is a valuable aid in determining the location of the intracranial injury and haemorrhage following head injuries. When one pupil was dilated the operation should be on the ipsilateral side.'[30]

C. Miller Fisher

With characteristic shrewdness, in 1995 Miller Fisher (1913-2012) investigated transtentorial herniation with computed tomography: descent through the tentorial opening could not be documented. Stressing the importance of lateral displacement, he warned that bilateral brain stem compression in acute bilateral cases must be distinguished from herniation:

> Upward cerebellar herniation is only the sign of an overfull posterior fossa. …Subfalcial herniation is tolerated unless lateral displacement is excessive…Combining clinical, pathologic, computed tomography and magnetic resonance imaging data, it is concluded that temporal lobe herniation is not the means by which the midbrain sustains irreversible damage in acute cases, but rather lateral displacement of the brain at the tentorium is the prime mover and herniation a harmless accompaniment.[31] The dilated pupil is attributed to midbrain distortion instead of uncal herniation.

Conclusion

It is scarcely necessary to conclude that in this context the mechanisms of abnormal pupils remain debatable since many fundamental questions still await solution. The unilaterally dilated pupil can be explained by stretching of the oculomotor nerve over the clivus or by its compression by a bulging hemispheric mass or haemorrhage. It appears that depression of consciousness is mainly related to a lateral brain shift at the tentorium. The false-localising impaired pupil reaction on the opposite side is attributed to midbrain damage due to distortion and compression.[32,25]

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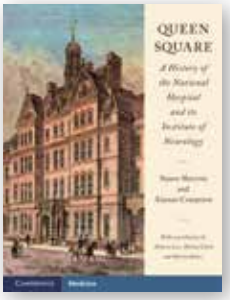
Queen Square. A history of the National Hospital and its Institute of Neurology



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Reviewed by: AJ Larner, Cognitive Function Clinic, WCNN, Liverpool.

There can be few neurologists, if any, unaware of the signification of "Queen Square" (although here in Liverpool it is synonymous with a bus station). It used to be said that there were two types of Neurologist – those who trained at Queen Square, and those who wished they had trained at Queen Square. Certainly many of the former and quite possibly many of the latter may be interested to consult this long awaited and limited edition history of an institution which some may still regard as the Neurology "mother ship".

The founding of the National Hospital in 1860 occurred at a time of developing interest in Neurology as an independent specialty (e.g. the work of Charcot and Vulpian at the Salpêtrière in Paris; Silas Weir Mitchell at the Turner's Lane Hospital in Philadelphia). Its origins were as a philanthropic endeavour funded by charity with unpaid honorary clinical appointments, from which has eventually evolved a research-intensive medical specialism. The journey documented here has evidently been a bumpy ride, with the hospital near closure on more than one occasion. Whilst the clinical contributions emanating from Queen Square are well known, the bureaucratic history provided here is certainly less familiar, and serves to remind us that the power struggle between clinicians and managers is not unique to our own times.

Great though the pantheon of QS alumni is, this book is no mere hagiography: although the greats are individually attended to (e.g. Hughlings Jackson, Ferrier, Gowers, Horsley, Holmes, Kinnier Wilson, Critchley, Symonds), this is also a carefully contextualised history, with much recourse to the minutes of the Board of Management and reference to contemporary historical events (hence, it is more than might have been anticipated from the book's title alone). The world wars in particular did much to shape the institution's history. The chapter on development of Neurology in the United Kingdom more widely is a welcome counterpoint; of course, Queen Square trainees accounted for much of the initial spread of neurological services.

This is a fascinating history, well told, with a uniformity of style despite the dual authorship and the (unspecified) contributions of three others (Andrew Lees, Michael Clark, Martin Rossor). The text is supplemented with footnotes, some quite extensive (e.g. biographical sketches of some of the notable, but not stellar, QS staff), black and white illustrations (some very evocative, such as the entrance hall where one sat before interview in the Boardroom, p41; the blackboards in the lecture theatre, p135; A-room, p458-9). There are occasional anecdotes, consistently engaging (e.g. Carmichael's self-experimentation on testicular pain, p441n4, was particularly eye-watering – researchers were made of stern stuff in those days!) and authorial asides.

It would be neglecting a reviewer's duty to forego a few minor criticisms, however nit-picking they may appear. There are occasional typographical and factual errors (particularly egregious: "Single Proton [sic] Emission Computed Tomography, p399; the date given for Anita Harding's graduation, 1995, is in fact the year she died, p474; "winter of discontent" ascribed to 1973/4, rather than 1978/9, p503n14); many seem to be in the footnotes. I was disappointed that in discussing Gowers as a possible source for Arthur Conan Doyle's Sherlock Holmes story *The Resident Patient*, the reference (p58n16) was to Lees' paper (Brain 2015;138:2103-8) but without mention of what I believe to be the original formulation of Holmes as Gowers (*The Sherlock Holmes Journal* 1992;20(4):128-30; Lees does not cite this paper, either) by Robin Howard and Hugh Willison, both of whom were working at QS at the time. The minutiae of ward life and the patient perspective are also absent, since unlikely to have been recorded for the benefit of posterity.

I found this book an immensely enjoyable read. The authors have produced a work which will stand as the definitive history for many decades. They deserve our thanks and congratulations for their labours. It is a book which I shall certainly return to in the future.

ACNR

My Chronic Migraine Story

Elaine Bell

Published online first: 15/2/19.
Provenance and peer review:
Invited and internally reviewed.

My migraines started when I was about 10 years old and it was at least 20 years before I was diagnosed with Chronic Migraine. Whilst I was diagnosed by my GP as suffering from migraine, the words Chronic Migraine were never mentioned although I had frequent visits to my GP looking for relief. It was only after doing my own research that I raised the possibility of Chronic Migraine with my GP and prophylactic treatment was prescribed.

I tried a number of prophylactic medications including Propranolol, Amitriptyline, Pizotifen, and Topiramate to name a few. I was unable to tolerate some of the side-effects associated with some of these medications. Brain-fog, no energy and feeling tired were not conducive to maintaining full-time employment. I was unable to concentrate and my memory recall seemed to be impaired much of the time. Pizotifen caused rapid weight gain which was not acceptable to me. I have always been an active individual enjoying sport, and until that point my weight had never been an issue. I tolerated Propranalol reasonably well and it seemed to help for a while, but after taking it for a couple of years I felt its effectiveness began to decline.

I recently turned 50 and all my life I have been advised by GPs that as I got older my migraines should decrease in severity and frequency. Unfortunately, this never happened. I probably have a genetic predisposition as my mother, grandmother and great grandmother all suffered. As a young child at school the only medication available to me was paracetamol, which I used to swallow by the bucket load, but it had no effect on my migraine at all. I can recall my grandfather when I was very young applying cold compresses to my head and using his hands to tightly hold my head in order to give me some relief.

My migraines are complex. Even after all these years as a Chronic Migraine patient, I am no further forward in identifying the main causes. I have learned through trial and error what to avoid; intense exercise, stressful situations, wine, citrus fruit and bright flashing lights to name a few. Even when I manage to avoid these triggers along comes an attack, apparently from nowhere, that will floor me for four or five days and I have no idea what has caused it.

Over the years I have become adept at masking my chronic pain from others, including my employer and those closest to me for fear of sounding like I am constantly complaining. To put this into context, I would suffer from this debilitating chronic migraine pain for more than half of any given month – the constant pulsating, throbbing pain in my temple and neck makes me feel nauseous; I find noise & light difficult to bear. I can't concentrate and sometimes find it difficult to form words. My bed, a dark room, an ice pack and a hot water bottle are all essentials.

Even though I realised that I was stuck cycling medications that didn't work I still lived in fear of running out of them. I used to feel guilty about requesting repeat prescriptions, as a GP once reminded me how much I was costing the NHS or on another couple of occasions, I was identified as one of the top users in the Practice when they were reviewing their prescribing patterns!

My relationship with the medical profession for decades until very recently has been a cycle of repeat prescription requests and very little by way of other possible alternative interventions. Occasionally, I would find I was in so much pain that I would end up in our local Out of Hours Service desperate for relief having had days of pain with nothing helping. At these times, I visited my GP to ask for a change in medication. This was always met with resistance and I would be sent off with another prescription and the cycle continued until the next time.

Fortunately, my attitude and experiences started to change with the advent of the internet and thereafter social media. This for me opened up a new world of other sufferers who had similar experiences. With interest I read Blogs, Twitter, Facebook, numerous helpful websites e.g. The Migraine Trust, Migraine Research Foundations, and The National Migraine Centre. I began to educate myself and then, several years ago, I attended a conference in Glasgow which had been advertised on the Migraine Trust's website.

Attending this conference was a catalyst for me; it changed my approach to my migraines and the support I received. I decided that day to take control and break the cycle of repeat prescriptions which had me living my life in almost constant pain. A Neurologist with an interest in headache at Southern General Hospital in Glasgow was the keynote speaker at the conference. With my GP's support, and through my husband's private healthcare programme, we arranged a referral to see him and with his help, I tried different treatment options. I was prescribed Topiramate as I hadn't tried it, but couldn't tolerate it at all. I also tried acupuncture which I understand helps some, but it didn't seem to work for me.

The only other thing that I try to do is to make a concerted effort to keep my sugar intake to as low a level as possible. I have no scientific reason for doing this, only an instinctive feel that it seems to help. I notice that when I indulge in eating high sugar foods my migraines can be triggered, but again that isn't 100% guaranteed.

My most recent treatment intervention, BOTOX (botulinum toxin type A), has been effective and my migraines have reduced significantly both in severity and frequency. After decades of missed family events, opportunities, work, education and social functions I am finally experiencing an overall improvement in the quality of my life and that of my family. I worry less about pending significant work or family events. I used to get very anxious about letting family, friends and work colleagues down. When my Chronic Migraine was at its worst, I had no control over my day to day living. Now I can plan, commit and enjoy for truly the first time without the worry of letting those close to me down.

What have I learned?

Like many patients, I always accepted my GP's advice in the early years of suffering from migraine. The advice was limited to "Your migraines will probably decrease as you get older and likely disappear after menopause". At that time, I was hugely naive about migraine, its symptoms and treatments. It was only when I started to educate myself by reading articles and attending events organised by the Migraine Trust that I began to understand my condition more. I requested that my GP refer me to a headache clinic. I asked to try specific treatments, took part in some trials. It was all trial and error. If I were to rewind the clock, I would not have sat back for so long and accepted repeat prescription after repeat prescription for so many years.

Only after 35 years of suffering mainly in silence have I now opened up more to my employer, friends and family about how frequently I suffer. This in itself has been therapeutic.

If I were to pass on my learning to anyone who has just been diagnosed, it would be to firstly educate yourself and those close to you. Be curious about your condition – there are lots of treatments options available, it's not a one-size-fits-all-condition. Seek support from specialist clinicians. Change GP if you feel you are not getting appropriately supported, be kind to yourself and finally, don't give up – there is help available.

Clinical perspectives on MAVENCLAD® (cladribine 10mg tablets), for highly active relapsing multiple sclerosis (MS), and real-world experiences from members of the multidisciplinary MS team

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Introduction prepared by Paula Kidgell, medical writer.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS). Consequential pathological changes such as inflammation, demyelination, and variable degrees of axonal loss and gliosis result in a multitude of distressing symptoms for people with MS, and have a significant impact on their quality of life.[1]

Advances in our understanding of the immunopathophysiology of the disease, and the pivotal role of both B lymphocytes and T cells, have led to significant developments in the treatment of MS. [1-4] As the treatment options for relapsing-remitting MS (RRMS) evolve, patients and clinicians alike are now able to make treatment decisions based on modes of administration as well as efficacy and safety.

One such advance is MAVENCLAD®, a synthetic small molecule which selectively targets B and T lymphocytes resulting in their transient reduction.[4]

MAVENCLAD® has been available in Europe for the treatment of adult patients with highly active relapsing MS, as defined by clinical or imaging features, since September 2017.[4] It has been suggested that MAVENCLAD® is classified as immune reconstitution therapy (IRT), because of its impact on key cellular components of the immune system.[1,4,9]

This MS-DIGEST paper summarises the key data from the MAVENCLAD® clinical development programme.[10-12] In a separate commentary, clinical experts from the multidisciplinary MS team share their thoughts on the clinical data and provide insights into real-world experiences of introducing MAVENCLAD® into clinical practice.

MAVENCLAD® clinical development programme

CLARITY is a 96-week, phase III, double-blind, placebo-controlled, multicentre trial, which aimed to investigate the efficacy and safety of MAVENCLAD® as an annual short-course oral therapy, in patients with RRMS (N=1326).[10]

Patients were randomly assigned to receive a cumulative dose of either 3.5mg/kg MAVENCLAD® or an unlicensed dose of 5.25mg/kg cladribine tablets or matched placebo. Each treatment course consisted of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consisted of 4 or 5 days on which the patient received one or two tablets as a single daily dose, depending on body weight [Figure 2].[10,11,12] Primary endpoint for the CLARITY study was rate of relapse over 2 years.[10]

Overall, 1184 patients (89.3%) completed the 96-week CLARITY study. This study demonstrated that MAVENCLAD® delivered consistent clinical and radiologic efficacy across the overall study population.[10]

Clinical efficacy

- A significant reduction in annualised relapse rates (ARR) over 2 years with MAVENCLAD®, versus placebo [0.14 versus 0.33, respectively], p<0.001.[10]
- Time to first relapse was 13.3 months (HR 0.46) in the MAVENCLAD® 3.5mg/kg treatment group, compared with placebo, 4.6 months (p< 0.001).[1]

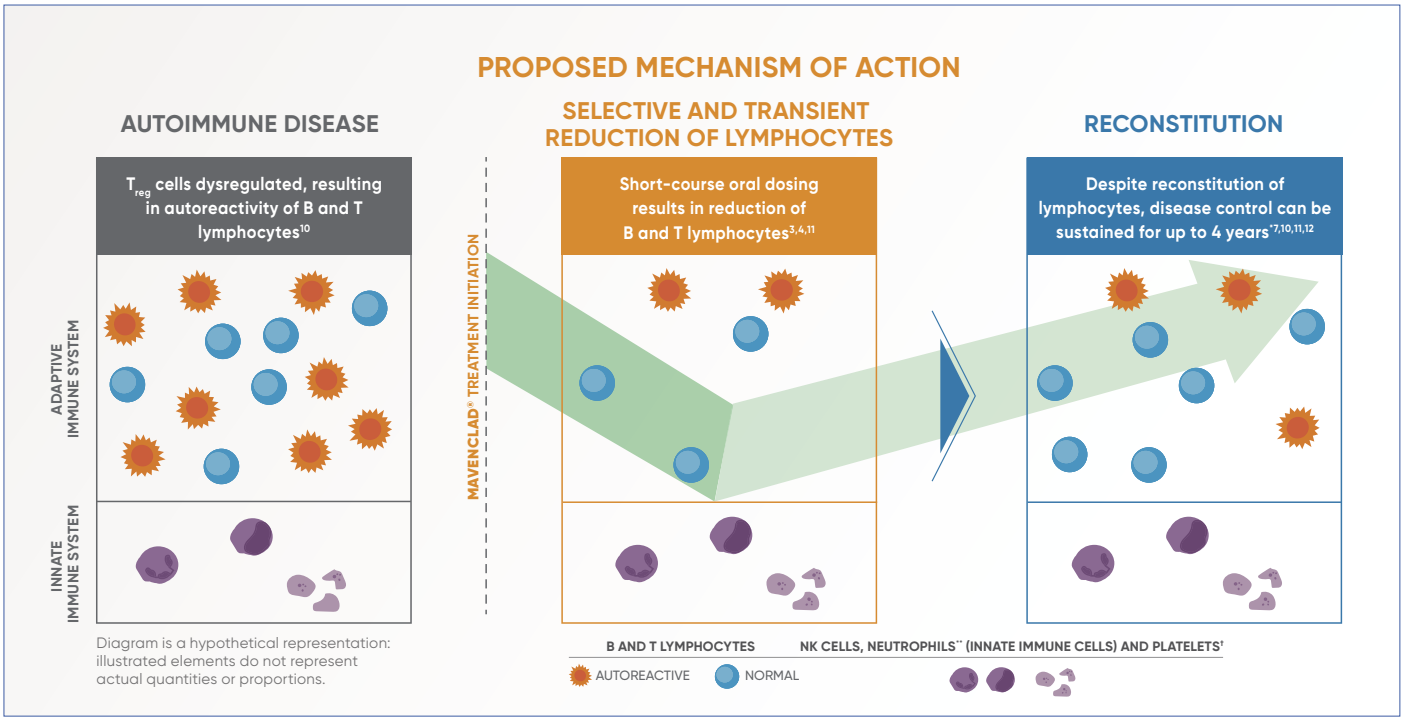


Figure 1. Schematic hypothetical representation of the mechanism of action by which MAVENCLAD® exerts its therapeutic effect in MS: illustrated elements do not represent actual quantities or proportions. [Adapted from 1,2,4–11]

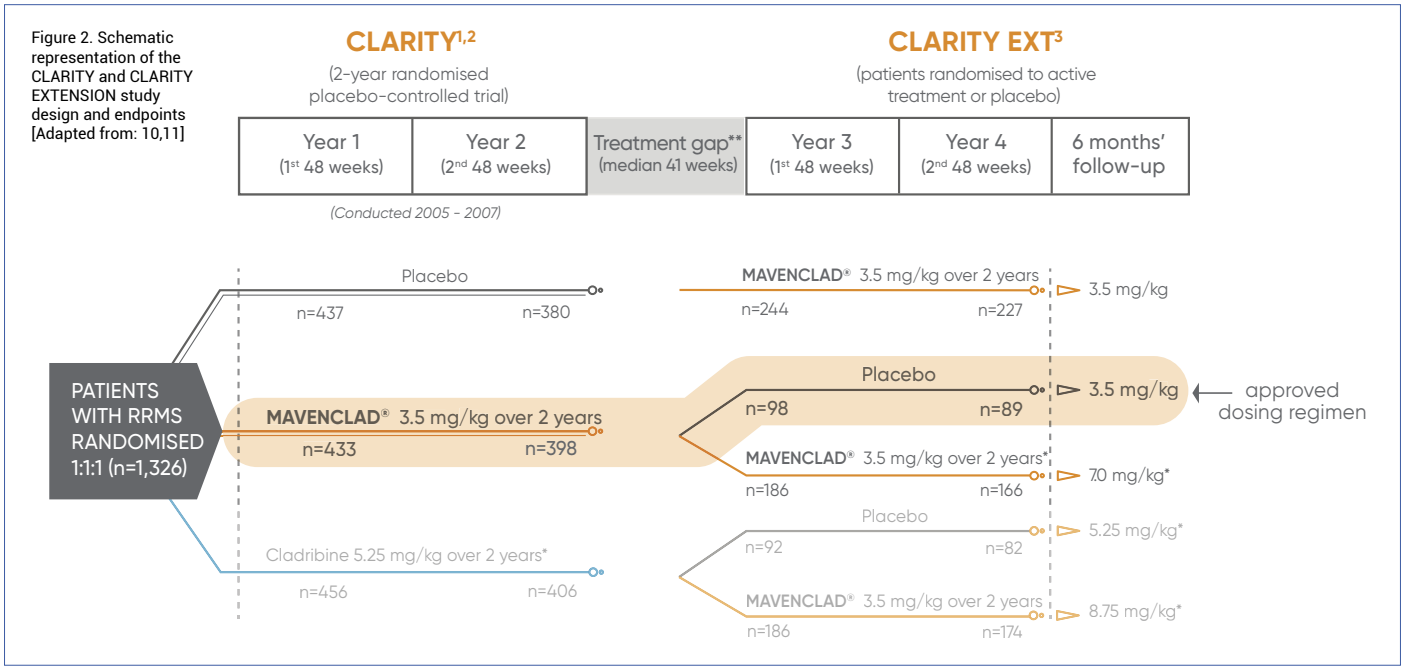


Figure 2. Schematic representation of the CLARITY and CLARITY EXTENSION study design and endpoints [Adapted from: 10,11]

- More patients were relapse-free for 2 years with MAVENCLAD®, versus placebo [79.7% versus 60.9%, respectively p<0.001].[10]
- MAVENCLAD® treated patients had a 47% risk reduction of 6-month-confirmed Expanded Disability Status Scale (EDSS) compared to placebo, p=0.0016, MAVENCLAD® [n=433] vs. placebo [n=437]. Time to 6-month EDSS progression: HR 0.53 (0.36 - 0.79)
- [post hoc analysis].[13]
- MAVENCLAD® treatment showed a significant relative reduction of 86% in T1 Gd-enhancing lesions (0.12), versus placebo (0.91) and a relative reduction of 73% in active T2 lesions on with Mavenclad (0.38), versus placebo (1.43) (P<0.001 for all comparisons).[1,4,10]

These data show that MAVENCLAD® treatment significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks, compared to placebo. The extension study (CLARITY EXTENSION)[11] which assessed safety over a further two-year period (without active treatment) [Figure 2], also demonstrated that the effect of MAVENCLAD® treatment may persist for up to four years.[11] 75% of patients (n=98) in CLARITY Ext receiving placebo (who originally received a cumulative dose of 3.5 mg/kg over 2 years in the CLARITY study) were relapse free in years 3 and 4 despite no further treatment after the first two treatment years.[11]

A post-hoc analysis of the CLARITY study assessed the treatment effects of MAVENCLAD® in the high disease activity (HDA) patient population, compared with the overall study population.[12] Results showed that MAVENCLAD® demonstrated an even greater effect in HDA patients versus non HDA patients.[12] Patients with highly active relapsing MS who received MAVENCLAD showed an 82% relative reduction in 6-month confirmed EDSS progression at 2 years [Hazard Ratio versus placebo for HDA population =0.18 (p<0.0001)], and a 67% relative reduction in annualised relapse rate (ARR) versus placebo [Relative Risk versus placebo for HDA population =0.33, (p<0.0001), MAVENCLAD® (n=140): 0.16 vs. placebo (n=149): 0.47].[12]

Safety

In the pivotal, phase III CLARITY study, incidences of the most commonly reported adverse events for MAVENCLAD® were comparable to placebo (8.4% for MAVENCLAD® versus 6.4% for placebo), with the exception of lymphopenia.[10] Due to its mechanism of action, transitory, mostly mild-to-moderate lymphopenia has been observed following active MAVENCLAD® treatment; 20%-25% of patients receiving MAVENCLAD® over 2 years developed transient Grade 3 or 4 lymphopenia.[4] However, most patients can be expected to recover to either normal lymphocyte counts or Grade 1 lymphopenia within 9 months.[4]

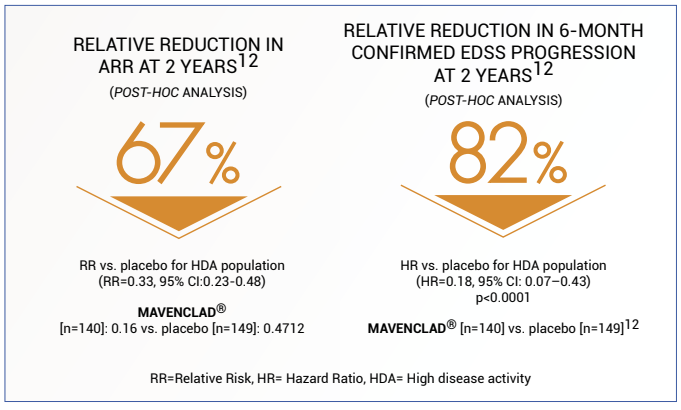
The most clinically relevant infection reported in MS patients who received MAVENCLAD® at the recommended cumulative dose of 3.5 mg/kg over 2 years in clinical studies was herpes zoster.[4] All cases of herpes zoster were dermatomal, and no case was disseminated. If such signs and symptoms occur, anti-infective treatment should be initiated as clinically indicated. Interruption or delay of MAVENCLAD® may be considered until proper resolution of the infection. There was no increased risk of opportunistic infections compared to placebo.[16]

To date, there have been no cases of secondary autoimmunity reported by cladribine treated patients in the PREMIERE registry.[17]

Events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo in the CLARITY trial.[4]

MAVENCLAD® is contraindicated in MS patients with active malignancies. An individual benefit-risk evaluation should be performed before initiating MAVENCLAD® in patients with prior malignancy.[4] Overall, there was no obvious pattern or cluster of specific tumour types or locations for either cladribine or placebo.[14]

A review of the malignancy risk for DMT treatments for MS by an academic group based in the UK compared published data from 2-year clinical studies and found that the malignancy rate of cladribine-treated subjects in the CLARITY study (0.34%) was not significantly different from all other active treatment groups (0.67%, p=0.3669) for other disease modifying therapies.[15]



The long-term safety of MAVENCLAD® continues to be monitored in clinical registries, which currently have up to 10 years' of safety follow-up.[17] Knowledge around the adverse events associated with MAVENCLAD® has helped to inform risk mitigation strategies prior to treatment initiation.[4,14] Overall, MAVENCLAD® is generally well tolerated with only 3.5% of MAVENCLAD® treated patients discontinuing treatment due to adverse events in the CLARITY study.[10]

MAVENCLAD® clinical data: The Consultant Neurologist's perspective – Dr Adrian Pace

Initial indications gathered from personal experience prescribing MAVENCLAD® to patients with MS in the first six months post-UK availability have been positive, confirming its reassuring tolerability regardless of patients' MS profile, and past experiences with other disease modifying therapies. From my initial cohort of patients we have not experienced any early recrudescence of their MS Symptoms.

Overall, available results from clinical studies position MAVENCLAD® confidently within the MS treatment algorithm for the management of patients with highly active relapsing MS.[12] In turn, eligible members of the MS community may now access a therapeutic option which marries high efficacy*, with a reassuring safety profile and the potential for reducing their disease progression over the four-year period.[12,18-20]

* High-efficacy, defined by the ABN as "[Disease-Modifying Therapies] with an average relapse reduction substantially more than 50%"[20]

MAVENCLAD® clinical data: The Consultant Neurologist's perspective – Dr Peter Brex

From the clinical practice perspective, MAVENCLAD® is a welcome addition to our arsenal of treatments available for people with RRMS. Patients treated with MAVENCLAD® initially attend an out-patient assessment with one of our MS nurses or MS pharmacist, where the benefits and potential risks are explained, active malignancy, active, chronic and latent infections are excluded, in women of childbearing potential, pregnancy must be excluded and a full blood count is taken to ensure the lymphocyte count is normal before the first course.[4] Vaccination is arranged for patients who are found not to have antibodies to varicella-zoster virus.

The supporting clinical data, as outlined above, show that the clinical benefits of the MAVENCLAD® treatment regimen can last for up to four years.[11] In addition, it is generally well-tolerated and there are no mandatory MRI monitoring requirements, except at pre-initiation, but we perform a baseline MRI and routine annual brain MRI subsequently to assess disease activity.[4]

I feel that MAVENCLAD® will be of particular benefit as first-line use for people with MS who present with high disease activity, or for those people who relapse on platform therapies.

MAVENCLAD® dosing regimen, treatment adherence and tolerability: The Neuroscience Pharmacist perspective – Joela Mathews

The oral dosing of MAVENCLAD® occurs at weeks one and five, administered in years one and two, as outlined in the CLARITY study. The exact number of tablets taken within each week uses a dose-banding principle based on weight and a cumulative dose of 3.5mg/kg over 2 years. The distribution of the total dose over the two years of treatment can be found in the Summary of Product Characteristics and in Table 1 below.[4]

Efficacy results from the CLARITY extension trial show that MAVENCLAD® can sustain up to four years of disease control, without the need for further treatment in years three or four.[11]

MAVENCLAD® is generally well tolerated, with good medication adherence over the short courses of treatment seen at our practice to date, which results in less pharmaceutical wastage.

Good compliance also helps to ensure that patients receive the maximum benefit possible from their treatment.

For some patients it is the reduced burden compared to other approved high-efficacy Disease-Modifying Therapies in a 4-year horizon, in terms of days on active treatment and monitoring, which may be of benefit to them. MAVENCLAD® offers a treatment option which allows patients to take treatment for up to 20 days over two years at home. MAVENCLAD® could also ease the burden on family members, who may have found their lives restricted in the past due to hospital transportation and giving injections.

Table 1. Dose of MAVENCLAD® per treatment week by patient weight in each treatment year.[4]

Weight Range	Dose in mg (number of 10mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
40 to <50	40mg (4 tablets)	40mg (4 tablets)
50 to <60	50mg (5 tablets)	50mg (5 tablets)
60 to <70	60mg (6 tablets)	60mg (6 tablets)
70 to <80	70mg (7 tablets)	70mg (7 tablets)
80 to <90	80mg (8 tablets)	70mg (7 tablets)
90 to <100	90mg (9 tablets)	80mg (8 tablets)
100 to <110	100mg (10 tablets)	90mg (9 tablets)
110 and above	100mg (10 tablets)	100mg (10 tablets)

MAVENCLAD® benefits to patients: The Clinical Nurse Specialist in MS perspective – Samantha Colhoun

MAVENCLAD® is an alternative treatment option for patients with highly active MS, offering a number of benefits along with the added reassurance from long-term safety data[14,17]. In addition to the clinical benefits already outlined above, MAVENCLAD® offers people with MS:

- A medication schedule that offers an opportunity for planning of pregnancy for women 6 months after the last dose in year 2 (note: MAVENCLAD® is contraindicated in pregnancy, please see full prescribing information for MAVENCLAD® fertility, pregnancy and lactation recommendations)[4]
- A short course oral treatment with low monitoring requirements
- A self-dosing regimen that can be taken at home at a time convenient to the patient, without the need to take time off from work

Alongside the benefits to patients, MAVENCLAD® has the potential to reduce demands on the NHS and current MS services. A reduction in the need for frequent monitoring or the need for infusions, could reduce the demands on infusion services, potentially resulting in long-term cost savings to the NHS.

Summary

MAVENCLAD® is the only oral immune reconstitution therapy that selectively reduces B and T lymphocytes with minimal impact on innate immune function.[1-4] Supported by robust clinical data, the annual therapy taken for up to 20 days over two years can provide disease control in patients with highly active relapsing MS, for up to four years, and is generally well-tolerated.[4,12]

An increased knowledge around the pathophysiology of MS is driving an era of effective treatment options for patients with the disease. Favourable developments in methods of administration allow for simple dosing regimens and low monitoring, helping to lessen the burden of the disease for people with MS.

Ease of administration and low monitoring burden, along with the efficacy and long-term safety data from clinical trials, means the benefits of MAVENCLAD® are now being seen by patients and members of the multidisciplinary MS team in 'real-world' practice.

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Cladribine tablets (MAVENCLAD®) funding and reimbursement

MAVENCLAD® has been approved for use by all relevant funding bodies in the UK and Ireland, which include Scottish Medicines consortium, NICE, AWMSG and HSE.

MAVENCLAD® cladribine tablets prescribing information (Please refer to the full Summary of Product Characteristics before prescribing). **PRESENTATION:** Cartons of 1, 4 or 6 tablets. Each tablet contains 10mg of cladribine. **INDICATIONS:** Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. **DOSAGE AND ADMINISTRATION:** Must be initiated and supervised by a physician experienced in MS treatment. Recommended cumulative dose: 3.5mg/kg body weight over 2 years, administered as one treatment course of 1.75mg/kg per year. Each course comprises 2 treatment weeks, one at the start of the first month and one at the start of the second month of each year. Each treatment week comprises 4 or 5 days on which the patient receives 10mg or 20mg as a single daily dose, depending on body weight. For details, see dosage tables in the SPC. No further cladribine treatment is required in years 3 and 4. **CONTRAINDICATIONS:** Hypersensitivity to cladribine or to the excipients; HIV infection; active chronic infection (tuberculosis or hepatitis); initiation in immunocompromised patients including those receiving immunosuppressive or myelosuppressive therapy; active malignancy; moderate or severe renal impairment (creatinine clearance <60mL/min); pregnancy and breast-feeding. **PRECAUTIONS:** Not recommended in moderate or severe hepatic impairment. Exercise caution in elderly patients. Determine lymphocyte counts before initiation in years 1 and 2, 2 and 6 months after treatment start in each treatment year. Count should be normal pre-treatment in year 1. If count below 500 cells/mm^3 at 2 or 6 months, actively monitor until values increase. If count below 800 cells/mm^3 pre-treatment in year 2, delay treatment. Stop treatment if recovery takes more than 6 months. Screen for latent infections prior to initiation in years 1 and 2. Delay initiation in latent or acute infection until treated. Varicella zoster vaccination is recommended in antibody-negative patients prior to treatment initiation. Delay initiation for 4-6 weeks following vaccination. Consider anti-herpes prophylaxis during grade 4 lymphopenia. If lymphocyte count falls below 500 cells/mm^3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt or delay MAVENCLAD® until infection has resolved. Perform baseline MRI before initiating MAVENCLAD® (usually within 3-months). Evaluate benefit-risk prior to initiation in patients with previous malignancy. Advise patients to follow standard cancer screening guidelines. Exclude pregnancy before initiation in years 1 and 2. Before initiation in year 1 and 2, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used by both male and female patients during treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraception should add barrier method during treatment and for at least 4 weeks after last dose in each treatment year. In patients previously treated with immunomodulatory or immunosuppressive products, consider their mode of action and duration of effect before initiation of MAVENCLAD®. Consider an additive effect on the immune system when such products are used after treatment with MAVENCLAD®. When switching from another MS agent, perform a baseline MRI. In patients requiring blood transfusion, irradiation of cellular blood components is recommended prior to administration. Not to be taken by patients with hereditary fructose intolerance. Separate administration of any other oral medicinal product by at least three hours from MAVENCLAD® administration. Concomitant treatment with other disease-modifying treatments for MS not recommended. Monitor haematological parameters when taken with other substances that affect the haematological profile. Do not initiate treatment within 4-6 weeks of live or attenuated live vaccines. Avoid vaccines during and after treatment while white blood cells not within normal limits. Avoid co-administration of ENT1, CNT3 or BCRP inhibitors during the 4-5 day treatment period. Consider possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered. **SIDE EFFECTS: Very common:** Lymphopenia **Common:** Oral herpes, dermatomal herpes zoster, decreased neutrophils, rash, alopecia **Other side effects:** Tuberculosis. In clinical studies and long-term follow-up, malignancies were observed more frequently in cladribine-treated patients compared to placebo. Prescribers should consult the Summary of Product Characteristics in relation to other side effects.

LEGAL CATEGORY: POM.

PRICE:
Pack of 1 tablet: £2,047.24
Pack of 4 tablets: £8,188.97
Pack of 6 tablets: £12,283.46
For prices in Ireland, consult distributor Allphar Services Ltd. Marketing Authorisation Holder and Numbers: Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands;
EU/1/17/1212/001, 002 & 004

For further information contact:
UK: Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373.
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Date of Preparation: August 2018
Job No: UK&IE/CLA/0818/0089

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Job No: UK&IE/CLA/0918/0103(1) | April, 2019

ABN Annual Meeting

Peter Fernandes
is a Clinical Lecturer in Neurology at the University of Edinburgh and ABNT regional representative for Scotland.

Samuel Shribman
is a Clinical Research Fellow in Neurology at University College London and ABNT Chair.

Edinburgh has been the capital of Scotland for many centuries and possesses a wealth of cultural and geographical attractions. Affectionately known as 'Auld Reekie' (for the smoke clouds that formerly plagued the city), Edinburgh is also known as the 'Athens of the North' for the topographical similarities between the cities, as well as the neo-classical architecture of the New Town.

The next ABN meeting will be held at the Edinburgh International Conference Centre (EICC) and will open with the ABN Trainee Day on Monday 20th May 2019. Previously known as the Pre-Meeting Day, this year it will incorporate the trainee forum and dinner to make the most of the largest annual gathering of neurology trainees in the UK.

There is an exciting programme lined with talks from Professor Hugh Willison and Dr Maria Farrugia on peripheral neurological diseases and Professor Jon Stone and colleagues on functional neurological disorders, from both the neurological and psychiatric perspectives. Dr Louise Davidson will be covering how to prepare for consultancy and, in parallel, Foundation Doctors will have sessions exploring life as a Neurologist, how to get in to neurology training and discussions around a series of fascinating cases. Delegates will join up for the trainee forum and the clinical skills laboratory led by the inspirational Dr Richard Davenport before Professor Martin Turner closes the programme with the research session exploring how to choose a project. Everyone will re-group for the trainee dinner in the heart of the city later in the evening.

Foundation Doctors will have sessions exploring life as a neurologist, how to get in to neurology training and discussions around a series of fascinating cases

The programme for the main meeting is equally impressive covering a diverse range of topics over the following three days. We will hear about cells and cellular therapies from the bench to the bedside, modern dilemmas in neurology and what to do next after pausing for thought. In addition to a wide range of special interest groups on individual subspecialties there will also be plenary sessions dedicated to movement disorders and epilepsy as well as the annual Gordon Holmes, ABN Medallist and Practical Neurology lectures. The ever popular clinico-pathological conference will be held on the last day with oral and poster presentations throughout the week.

Edinburgh itself

Edinburgh is split between the aforementioned New Town (a relatively recent 18th-19th century construction) and the mediaeval Old Town, a rabbit warren of small winding streets (rather appropriately named 'wynds') surrounding the Royal Mile. This street, which connects Edinburgh Castle to Holyrood Palace and the Scottish Parliament, often hosts street performers, especially during the famous Edinburgh Festival Fringe in August.

Arthur's Seat, an extinct volcano just 1 mile from the castle (and which other city boasts a volcano within its limits?) is not difficult to climb and boasts fantastic views from the summit, including of the iconic Forth Bridge, accompanied by its two companions, the Forth Road Bridge and the recently completed Queensferry Crossing. Calton Hill is a worthy alternative, possessing the Scottish National Monument (a half-finished Parthenon-esque structure adding further weight to the Athens of the North sobriquet) and hosting the Beltane Fire Festival in April each year. Other nearby attractions include Portobello beach with golden sands (and freezing surf) upon which the Aurora borealis may be glimpsed if one is fortunate. Towards the south of the city Craigmillar Castle is famous for hosting Mary Queen of Scots, whose French retainers gave the surrounding area, now including the main Edinburgh hospital, its name of 'Little France'.

Edinburgh is also famed for its many illustrious citizens, many of whom lived during the Scottish Enlightenment in the 18th and 19th centuries. These include Adam Smith (whose 'invisible hand' underpins modern economic theory), David Hume, and the writers Arthur Conan Doyle ("elementary my dear Watson"), Robert Louis Stevenson (Treasure Island), Walter Scott (whose novels gave Waverley train station its name), and not forgetting JK Rowling of course, who still lives in the city. Scientists are not excluded, with James Clerk Maxwell, Alexander Graham Bell, and Ian Wilmuts all residents at one time or another (and the latter's most famous creation, Dolly the Sheep, can be found in the National Museum of Scotland – itself well worth a visit). From a medical perspective both Joseph Lister, who pioneered anti-septic use in surgery, and James Young Simpson, who introduced anaesthetics, were Edinburgh-based doctors. Finally, Greyfriars Bobby, the devoted hound who waited 14 years by the grave of his owner, is commemorated in the statue to be found near George IV Bridge.

With such a fantastic programme in a city centred on a UNESCO world heritage site and steeped in history and culture, the ABN meeting in Edinburgh will be a difficult one to miss. We hope to see you there!

PREVIEW: ABN Annual Conference 2019

Conference details: ABN Annual Conference 2019, Training day 20th May, Main meeting 21st-23rd May, 2019; Edinburgh, UK.
Report by: John Sussman, Meeting Secretary.


Jon Sussman

Edinburgh has been the capital of Scotland since at least the 15th century. Affectionately nicknamed Auld Reekie, it is also described as the Athens of the North as a result of the Greek Revival buildings, including the Surgeon's hall, with Castle Rock performing a similar role to the Acropolis.

Scotland is often viewed through the prism of the Scottish Enlightenment, though the first education Act of 1496 introduced compulsory education for the eldest sons of nobles, followed by the truly innovative Education act of 1696 providing for a school and a schoolmaster in every parish in Scotland. Perhaps it's not surprising that the first medical school in the UK was founded in Edinburgh in 1726, and that Scottish medicine, not to mention associated body snatching has led the world, resulting in the 1832 Anatomy Act, as well as a pantheon of leading clinicians including Robert Whytt, Charles Bell and the Monro trio.

It is therefore fitting that British neurology pays homage to our history with a return visit of the ABN to Edinburgh. The venues are all easily accessible and within easy walking distance of Edinburgh Haymarket Station on the main line from The South.

The conference opens on Monday 20th May with the Foundation Doctor Session and the ABNT Registrar Training day, including a research workshop. We are also holding an Acute Neurology training day in association with the Society of Acute Medicine.

We are delighted to announce that Pam Shaw is the 2019 ABN Medallist, "Translational neuroscience to improve outcomes for motor neurone disease: the blessings and challenges of the journey". On Tuesday 21 May, Charles Thornton from Rochester, New York Medicine will deliver the 25th Gordon Holmes lecture on prospects for developing treatment for myotonic dystrophy. David Burn, our President from 2019-2021 will deliver his President's Lecture "Walking the wheel the wrong way". In addition, Robin Ferner will deliver the Practical Neurology lecture on Thursday morning, on Harm from Medicine.

The Special Interest Groups will run sessions on Wednesday and Thursday mornings. This meeting's SIGs include, Functional Disorders, Myasthenia Gravis, Neuroncology, Motor Neurone Disease, Multiple Sclerosis and Neuroinflammation, and Headache. The SIG meetings offer an opportunity to hear updates in the field, to discuss interesting cases and meet with friends and future clinical and research collaborators.


Edinburgh Castle

The plenary sessions this year features Cells and Cellular Therapies: from bench to bedside, Epilepsy, Movement Disorders, Modern Dilemmas and "Pause for thought... What should I do now?" Once again there'll be a CPC in which you can pit your wits against a tricky case, which will seem all too obvious once you have the answer.

2019 has yet again seen another record number of abstracts submitted, assisted by the early career researcher abstract bursary, and we will have six parallel platform sessions and two guided poster sessions in addition to the ever-popular case presentations competition.

The Annual General Meeting will be held on Wednesday 22 May at 14:15. The Gala dinner will be held in the Stables at Prestonfield in a beautiful setting dominated by Arthur's Seat and Salisbury Crags to the east.

In addition, we have a fun run and a historic walking tour of Edinburgh. We hope you enjoy the meeting in this stunning setting.

Monday 20 May – Training Day – Neurology Trainees and Foundation Doctors			
Neurology trainee session		**Foundation doctors session**	
1230	Registration	1230	Registration
1300	Talk 1: Guillain-Barré Syndrome Hugh Willison	1300	What neurologists do and why Tom Warner
1335	Talk 2: Myasthenia Gravis Maria Farrugia	1330	Case-based discussions Ed Newman
1410	Preparing for consultancy Louise Davidson		
1430	Tea break	1425	Tea break
1450	Talk 3: Functional disorders – neurologists Jon Stone	1450	How to get into neurology training Diane Swallow
1525	Talk 4: Functional disorders – neuropsychiatrists Alan Carson	1535	Video Session Matt Jones
1605	ABNT Forum	1605	ABNT Forum
1640	Reception, light refreshments	1640	Reception, light refreshments
1700	Clinical Skills lab Richard Davenport	1700	Clinical Skills lab Richard Davenport
1745	Research session Martin Turner	1745	Research session Martin Turner
1815	End	1815	End

Tuesday 21 May		
09:00	**Opening and Welcome**	
09:15	**Plenary session 1: Cells and Cellular Therapies: from bench to bedside** • iPS stem cells as models of disease: Siddharthan Chandran, Edinburgh • Bone marrow - a real prospect: Martin Duddy, Newcastle • Neurology of CAR-T therapies: Claire Roddie, London	
10:45	Coffee & Exhibition 1	
11:15	Parallel session 1: Clincal Neurology 1	Parallel session 2: Quality
12:30	Lunch, Exhibition	
	Teva Symposia 1	Actelion Symposia 2
14:00	**Gordon Holmes lecture** Charles Thornton, Rochester New York – Prospects for developing treatment for myotonic dystrophy	
14:45	Parallel session 3: Phenotype & Genotype	Parallel session 4: Treatments – Looking to the future
16.00	Coffee & exhibition 2	
16:30	**Plenary session 2: Epilepsy** • Gene therapy and epilepsy Sudep Mechanisms: Matthew Walker, London • Drugs and epilepsy: New and old [Valproate/cannabis]: John Paul Leach, Glasgow • Epilepsy: How far do you go? [genes, antibodies]: Anthony Marson, Liverpool	
18:00	**Poster session with discussants 1**	
19.00	Drinks reception + posters + research opportunities forum	

Wednesday 22 May			
07:45	**Functional disorders SIG 1**	**Myasthenia Gravis SIG 2**	**Neuro-oncology SIG 3**
09:00	**Plenary session 3:** Movement disorders • When the honeymoon's over: new drugs in PD: Carl Clarke, Birmingham • Sleep and neurodegeneration: Paul Reading, Middlesbrough • Dystonia: Tom Warner, London		
10:30	Coffee and Exhibition 3		
11:00	**Poster session with discussants 2**		
12:00	**ABN Medallist lecture:** Pamela Shaw, Sheffield: Translational neuroscience to improve outcomes for motor neurone disease:the blessings and challenges of the journey. Citation: Chris McDermott		
12.45	Lunch, Exhibition		
	Novartis Migraine Symposium 3	Merck MS Symposium 4	
14:15	**AGM + Business session**		
15:45	Coffee and Exhibition 4		
16.15	**Plenary session 4:** Modern dilemmas – Chair: David Burn, Newcastle • Jacqueline Palace, Oxford • Uma Nath, Sunderland		
17:15	**President's lecture:** David Burn, Newcastle – Walking the wheel the wrong way		
18:00			
19:00	**Gala Dinner:** The Stables, Prestonfields		

Thursday 23 May			
07:45	**Motor Neurone Disease SIG 4**	**Multiple Sclerosis & Neuroinflammation SIG 5**	**Headache SIG 6**
09:00	**Case presentation competition**		
10:15	**Practical Neurology lecture** – Robin Ferner, Birmingham – Harm from medicines		
11:00	Coffee and Exhibition 5		
11:30	Parallel session 5: Neurological Treatment	Parallel session 6: Clinical Neurology 2	
12.45	Lunch, Exhibition		
	Novartis MS Symposium	Biogen Dementia Symposium	
14:15	**Plenary session 5:** Pause for thought...What should I do now? • Dilemmas and the spinal cord: Geraint Fuller, Gloucester • Neurology in the tropics – A Sri Lankan experience: Thashi Chang, President ASN • Thunderclap headache: Can I send this patient home?: Nicola Giffin, Bath		
15:15	**CPC**		
16.00	Top 5 posters		
16:45	Prize presentations and close		

To list your event in this diary email Rachael@acnr.co.uk by 31st May, 2019

2019

APRIL

Biomarkers in Neurodegenerative Diseases
2-5 April, 2019; UCL, Queen Square, London
E. r.paterson@ucl.ac.uk
https://bit.ly/2P5JbS1

Annual Head Injury Study Day 'Mild brain injury – 'The emerging picture'
4 April 2019; Derby, UK
www.ncore.org.uk
T. 01332 254679, E. dhft.ncore@nhs.net

The London-Innsbruck Colloquia on Status Epilepticus and Acute Seizures
7-9 April, 2019; London,UK
www.statusepilepticus.eu

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Benign & Metastatic Tumours
11 April, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

MAY

International Congress on Neuropathic Pain (NeuPSIG)
9-11 May, 2019; London, UK
www.iasp-pain.org
E. IASPDesk@iasp-pain.org

10th International Meeting of the Society for Research on the Cerebellum and Ataxias
16-17 May, 2019; Sheffield, UK
www.thesrca.org
T. +32 2 880 99 90, E. SRCA@semico.be

Association of British Neurologists (ABN) Annual Meeting 2019
21-23 May 2019; Edinburgh, UK
www.theabn.org/events/forthcoming-abn-events/abn-annual-meeting-2019.html

JUNE

Matthew's Friends KetoCollege
4-6 June, 2019; East Grinstead, UK
www.mfclinics.com/keto-college
E. ketocollege@mfclinics.com

Oxford Autoimmune Neurology Meeting 2019
5-6 June, 2019; Oxford, UK
E. gemma.pimentel@ndcn.ox.ac.uk
https://bit.ly/2sHJDwV

Dementia MasterClass
6 & 7 June, 2019; Sheffield, UK
dementiaacademy.co

Children's Headache Training level 1 (CHaT1)
Friday 7 June, 2019; Leeds, UK
https://courses.bpna.org.uk/

Modern Thinking in MS Management
7-8 June, 2019; Radisson Blu Portman Hotel, London
An educational meeting organised and funded by Teva UK Limited, open to Consultants, Nurses and Specialist Registrars with an interest in Multiple Sclerosis
www.modernthinkinginms.com
E. registration@modernthinkinginms.com

MS Intermediate MasterClass
12-14 June 2019; Halifax Hall, Sheffield, UK
https://multiplesclerosisacademy.org/events/ms-intermediate-master-class-8-module-1/

Parkinson's Academy: Parkinson's Advanced MasterClass
18-20 June 2019: Halifax Hall, Sheffield, UK
https://parkinsonsacademy.co/events/parkinsons-advanced-masterclass-36a-module-1/

Training in Behavioural Treatment for Tics (CBIT)
27-28th June, 2019; London, UK
E. Seonaid@tourettes-action.org.uk
www.tourettes-action.org.uk

The 5th EAN: Neuroinflammation – Science. Synergies. Solutions.
29 June – 2 July, 2019
www.ean.org/Oslo2019

JULY

British Neuro-Oncology Society Annual Meeting
3-5 July, 2019; London, UK
www.bnos.org.uk

MS Service Provision in the UK 2019: Raising the Bar
8 & 9 July, 2019; Birmingham, UK
multiplesclerosisacademy.org

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Neurotoxicity, Late effects, Rehabilitation & Ethics
11 July, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

SEPTEMBER

Building the future of childhood brain injury: where do we go from here?
Friday 6 September, 2019; London, UK
www.thechildrenstrust.org.uk/conference

British Neurotoxin Network (BNN) Annual Meeting 2019
12-13 September, 2019; Lady Margaret Hall, Oxford, UK
www.neurotoxinnetwork.org
E. info@neurotoxinnetwork.org

Tourettes Action Research Network (TARN) meeting 2019
Friday 13 September, 2019; 9:30-4:30, London, UK
www.tickettailor.com/events/tourettes-action/222723

Parkinson's Academy: Parkinson's Foundation Masterclass
19 & 20 September 2019; Halifax Hall, Sheffield, UK
https://parkinsonsacademy.co/events/parkinsons-foundation-masterclass-37f/

OCTOBER

Joint meeting of the Society for Research in Rehabilitation and the British Society of Rehabilitation Medicine
14-15 Oct 2019, 2019; University of Warwick, UK
www.srr.org.uk

NOVEMBER

MSologists MasterClass
Module 1: 6-8 November 2019
Module 2: 21 & 22 May 2020; Sheffield, UK
multiplesclerosisacademy.org

Expert to Expert: Epilepsy
For paediatric neurologists and other seeing children with epilepsy at tertiary level
28-29 November, 2019; Manchester, UK
https://courses.bpna.org.uk/ecomm_product_view.php?courseid=393

Karalyn Patterson awarded 2019 British Neuropsychiatry Association Medal

Karalyn Patterson has been awarded the 2019 British Neuropsychiatry Association Medal for the field-defining work she has conducted in Cambridge over more than four decades. Karalyn's work has become a blueprint for cognitive neuropsychology, as she has continually developed and adapted cutting edge behavioural, neuroimaging and statistical approaches to relate brain structure to function. She has been particularly influential in defining the syndrome of semantic dementia. In turn, this has defined our modern understanding of the brain basis of semantic memory, with anterior temporal lobe acting as a computational hub, binding together factual knowledge stored throughout association cortex.

Karalyn is hugely loved and respected within the cognitive neuroscience community. She has nurtured and developed generations of scientists, and is consistently humble about continuing and lifelong influence on their careers. She continues to work, applying her expertise to the care of patients with neurodegenerative aphasias in the frontotemporal clinic and collaborating in cutting-edge research on the brain basis of language at the MRC Cognition and Brain Sciences Unit, and the Cambridge Department of Clinical Neuroscience.

Karalyn's medal lecture, entitled "The Language Disorder in Semantic Dementia: Does it matter which language you speak?" delivered a scintillating overview of her decades of ground-breaking, collaborative work between England and Japan, demonstrating the language-independence of the semantic memory system, and the striking similarity of the cognitive pro-file in semantic dementia across contrasting cultures and linguistic backgrounds.

A million pound effort to tackle Lewy body dementia

The Lewy Body Society, a charity dedicated to tackling the second most common form of dementia, has announced the latest recipients of its grants programme. The charity is awarding three grants totalling £314,000 for projects at the University of Cambridge, Newcastle University and Imperial College London.

These grants take the total research funding issued by the charity to over £1 million, since it supported its first PhD student in 2007. All of the charity's funding is received from voluntary donations and earned income, and it receives no statutory funding.

The Lewy Body Society is now seeking applications for its next round of funding. The charity will consider any application that is relevant to Lewy body dementia, and applicants from UK institutions can apply for project funding, or to fund PhDs or fellowships. In this funding round, the society has up to £500,000 to allocate and will aim to fund 2 – 5 projects.

For information on the 2019 Grant Round visit https://www.lewybody.org/grant-round-2019. The deadline for applications is 31st May 2019.

UCL Institute of Neurology Advanced Stroke Neuroimaging Course

Conference details: 31st October, 2018, London, UK. ***Report by:*** Dr Milo Delaney MB BCH BAO, SHO in stroke medicine UCLH. ***Conflict of interest statement:*** Dr Milo Delaney is currently a stroke SHO at UCLH, employed by the trust.

As an SHO working in stroke medicine, I wanted to gain more knowledge on stroke neuroimaging in a structured learning environment from experts in the area. This interesting and informative one day course was perfect for my aim and exceeded my expectations.

The course is based in central London, at the UCL Institute of Neurology in Queen Square, adjacent to the National Hospital for Neurology and Neurosurgery. The course covered the various imaging modalities available to evaluate and treat ischaemic and haemorrhagic stroke along with the related neuroanatomy, through lectures and interactive case-based discussions.

Structure of the day:
- Time: 09:00 – 17:00.
- Breaks: 11:00 – 11:30, 12:45 – 13:45 (lunch provided).
- Cost: £150 early bird, £200 otherwise.
- Date: late October / early November every year.

The day started with an introduction to the practical use of neuroimaging in the assessment of a person presenting with stroke-like symptoms to the emergency department. The pathway through hyperacute care including initial clinical assessment, initial imaging and interpretation and then hyperacute treatment were outlined, especially useful for allied health professionals and aspiring stroke physicians.The specific case used illustrated the mechanical thrombectomy (MT) pathway – the relevant early imaging revealing the target for reperfusion - and the challenges in delivering this proven life-saving and disability-limiting treatment.

The next talk, entitled 'anatomy of the cerebral circulation', covered the basics of the intracranial vasculature from origins to terminal branches, and to the intracranial venous system. The talk systematically discussed each blood vessel and included an especially useful section on the more commonly encountered anatomical variants. Next, we learned about the imaging in acute infarction in each territory keeping the session clinically relevant and clarifying the neuroanatomical basis of the different stroke syndromes.

'Neuroimaging 1: ischaemic stroke' was the last talk of the morning. It covered the underlying pathophysiology of acute stroke and the resultant early imaging changes. The nuance of these subtle early and hard-to-identify signs was clearly explained in simple terms, this included the Alberta Stroke Programme Early CT Score (ASPECTS) – a vital tool which directs which patients might benefit for endovascular treatment. CT perfusion was also explained with its applications, such as wake-up stroke. MRI was also covered including perfusion and vessel wall imaging. The talk concluded with imaging stroke mimics, a rarely thought of topic.

Professor Werring (Professor of Stroke Medicine, ION), next gave a talk which covered all things intracranial haemorrhage (ICH) from the epidemiology, to basic aetiology and pathophysiology. The imaging modalities covered included CT, MRI blood-specific sequences and digital subtraction angiography (DSA). The imaging features within each modality were linked to specific aetiologies, and outlined the challenges in deciding which patients require early DSA so as to determine the aetiology of their ICH and reduce the risk of recurrence. The pillars of ICH management and the evidence basis for this concluded this talk.

After lunch we received talks on mechanical thrombectomy. Dr Perry (Stroke Neurologist and Research Lead, UCLH), guided us through the natural history of the evolving evidence base for thrombectomy, from trials which initially showed no benefit, to those which proved it to be one of the most efficacious treatments available in modern medicine. The final trials discussed were particularly exciting, proving efficacy of thrombectomy even after six hours from onset of symptoms.

Dr Robertson (Interventional Neuroradiologist, NHNN) spoke about the practicalities of delivering thrombectomy, the indications and the correct imaging choices. Dr Robertson highlighted the magnitude of the mismatch between the prevalence of stroke and the national provision of thrombectomy services, that depending on a patient's location or time of day, they might not receive this intervention.

The opportunity was then given to the attendees to present cases from our own trusts and experience, with discussion with the teaching faculty. This allowed a myriad of clinical dilemmas we had all encountered and struggled with to be discussed with experts in the area in a panel chaired by Dr Simister (Stroke Clinical Director, UCLH).

The last talk of the day focused on language recovery after stroke and how it can be illustrated using imaging. Three trials were presented providing an evidence base for the complex nature of language impairment and recovery following stroke.

The day concluded with a quick wrap-up of the course provided by Prof Werring, reinforcing the main points from each talk. The day surpassed my expectations in terms of the content, and delivery from experts in the field, based in an institution which is involved in emerging new and exciting approaches to stroke neuroimaging. Course materials were made available to all attendees to use as a reference point in the future. I would recommend this course to any health professional interested in working in stroke, to develop your knowledge of the applications of imaging in stroke medicine.

Encephalitis Society Conference 2018

Conference details: 3rd December, 2018, London, UK. ***Report by:*** Cory Hooper, University of Liverpool and edited by Dr Ava Easton, Encephalitis Society. ***Conflict of interest statement:*** None declared

On December 3rd, 2018, over 100 healthcare professionals congregated in London for the Encephalitis Society's 2018 conference. This was my first attendance, and with delegates from over 13 countries it was clear this was an international affair, attracting exceptional researchers, scientists, clinicians and professions allied to medicine. Throughout the day the packed house were captivated with a series of speakers representing a wide-range of disciplines including neurology, neuropsychology, neuroscience, sociology, and psychiatry.

Chaired by Professor Tom Solomon, the opening address entitled "Anti-NMDAR encephalitis: symptoms, mechanisms and disease models" was presented by keynote speaker Professor Josep Dalmau. Professor Dalmau began by discussing the relationship between structural brain changes and neuropsychological outcomes. The hippocampi appear to play an important role in anti-NMDAR encephalitis with hippocampal connectivity correlating with memory and hippocampal atrophy correlating with disease duration and severity. Professor Dalmau then presented findings of a recent study suggesting that herpes simplex virus encephalitis (HSVE) can precede autoimmune encephalitis which leads to neurological worsening. In this prospective study 27% of patients with HSVE developed autoimmune encephalitis and all presented with new neuronal antibodies. A large proportion of these antibodies (64%) were shown to be targeting the NMDA receptor suggesting a specific mechanism by which HSVE can lead to anti-NMDAR encephalitis. Professor Dalmau concluded his presentation by discussing how the field of immunology will play an important role in developing an active model of immunisation and the role of neuroscience in elucidating the role of NMDA brain networks.

Following the keynote address, Dr Adam Al-Diwani presented his work demonstrating the role of psychiatry in the early stages of anti-NMDAR encephalitis. Patients with anti-NMDAR encephalitis often present with psychiatric symptomology leading to frequent misdiagnosis resulting in delayed treatment. Dr Al-Diwani's research focuses on identifying the characteristic psychiatric features of anti-NMDAR encephalitis. Indeed, if potential anti-NMDAR encephalitis can be identified based on characteristic psychiatric symptomology time to correct diagnoses can be reduced and clinical outcomes improved.

Ms Raia Blum from the Department of Neurology at the Icahn School of Medicine in New York presented her work on the psychosocial outcomes of autoimmune and infectious encephalitis. Ms Blum reported persistent neurological symptoms and worsened psychosocial functioning in patients with autoimmune and infectious encephalitis. Importantly, this research highlights specific areas of psychosocial functioning that are affected by encephalitis which could lead to targeted, long-term psychosocial interventions to support individuals with encephalitis in the community.

L-R: Hayley Hardwick (second left) and Dr Sylviane Defres (second right) receiving awards for Excellence in Encephalitis Healthcare from Prof Tom Solomon, Dr Nicholas Davies, and Dr Ava Easton.

L-R: Oral presentation Award Winners: Amanda Tomlinson, Raia Blum, receiving awards from Prof. Josep Dalmau, Dr Susan Hills.

Ms Amanda Tomlinson, a medical student from the Icahn School of Medicine, presented research on the transition of patients with autoimmune and infectious encephalitis and its impact on caregivers. Specifically, Ms Tomlinson reported that caregivers are dissatisfied in the transition from inpatient to outpatient care and experience high levels of caregiver strain. Ms Tomlinson concluded the presentation with a call for more research on these important aspects of patient care.

After a short break, Dr Bonnie-Kate Dewar chaired the second morning session and introduced the first speaker Dr Sylviane Defres. Dr Defres engaged the audience with preliminary data from the ENCEPH-UK project, a large, multicentre programme aimed to understand and improve outcomes for patients affected by encephalitis. Prompt diagnosis and treatment administration is important for disease outcome in encephalitis. The findings from

the ENCEPH-UK study showed differences between different types of encephalitis in relation to hospital admission and commencing treatment and differences in the outcomes.

Ms Julia Griem also presented outcomes from the ENCEPH-UK study on neuropsychological outcomes. Despite significant advancements in the treatment and management of different forms of encephalitis patients are almost always left with neuropsychological deficits. Of further note was the discrepancy between objective measures and subjective reports, especially at >1 year post-illness: objective tests showed overall little neuropsychological impairment but patients reported high subjective complaints. Ms Griem provided a succinct summary of the neuropsychological sequelae associated with encephalitis showing that memory impairments correlate with medial temporal lobe damage.

Asst Professor Michael Wilson presented "Clinical metagenomic next-generation sequencing (MNGS) for diagnosis of infectious meningitis and encephalitis." Professor Wilson's presentation focused on demonstrating the efficacy of MNGS in identifying the aetiology of meningitis and encephalitis. Numerous viruses, autoantibodies, bacteria, fungi and parasites have been identified and shown to cause encephalitis. However, in approximately half of cases no cause can be identified. The novel application of MNGS in relation to encephalitis and meningitis could help identify infectious aetiologies in idiopathic cases. Professor Wilson illustrated this via a case study of Hepatitis E Virus (HEV) associated meningoencephalitis in a lung transplant recipient, diagnosed through clinical metagenomic sequencing.

To conclude the morning session Dr Lance Turtle presented his research on the diagnosis of acute encephalitis syndrome in South India. Dr Turtle described the challenges inherent in obtaining a microbiologic diagnosis whilst conducting research in Bellary and Bangalore, which included several logistic and clinical issues in processing samples for diagnostic testing. Unfortunately, such problems are common in South India resulting in many patients not receiving a specific diagnosis.

Following lunch, Dr Nick Davies chaired the first afternoon session and introduced Dr Susan Hills from the United States Centers for Disease Control and Prevention (CDC). This keynote presentation focused on the changing epidemiology of arboviral encephalitis. Dr Hills presented data gathered at the CDC showing the number of vector borne diseases in the US has tripled in the period from 2004 through 2016. This corroborates international research demonstrating a rapid emergence of arbovirus diseases globally. Dr Hills also presented information on arboviruses long recognised as causing encephalitis but with changing epidemiology, including West Nile virus, Powassan virus, and Japanese encephalitis virus. Finally Dr Hills described several arboviruses that have emerged in recent years which are not primarily arboviruses causing encephalitis but which can present with neurologic presentations, including chikungunya virus and Zika virus. She noted that new non-vector-borne mediums of transmission for Zika virus have been recognised since 2015 such as sexual transmission and intrauterine transmission, and possibly transmission through blood transfusion and breast milk.

Following the keynote address, Dr Ava Easton, Chief Executive of the Encephalitis Society presented three cases of Japanese encephalitis in returned UK travellers. This thought-provoking talk was a welcome reminder why many of us attending the conference are dedicated to preventing encephalitis and improving outcomes for patients. The three individuals presented all received significant support from the Encephalitis Society and this talk provided a sobering reflection on the remarkable work conducted by the Society.

Dr JM de Vries presented "Mimics of autoimmune encephalitis - a retrospective cohort study". The diagnostic criteria for autoimmune encephalitis (AE) is heavily reliant on antibody testing, and immunotherapy response which might impede a prompt diagnosis. Recent research has focused on improving provisional diagnosis to improve immediate treatment options which has resulted in the development of a 'probable AE' category. In the recently published criteria for AE (Graus et al, 2016) also a novel diagnosis of 'probable seronegative AIE' is included, a diagnosis by exclusion based on strict criteria. Dr de Vries showed that within the group of presumed seronegative AE, mimics are important to consider as treatment and prognosis differ. As none of the 40 AE mimics fulfilled the Graus criteria for probable seronegative AE, these criteria seem valid. Among the AE mimics, the most frequent diagnosis were central nervous system (CNS) inflammatory disorders and CNS infections. Disconcerting were the CNS malignancies mimicking AE. In 7 AE mimic patients a cerebral biopsy was indicated to make a final diagnosis, in four of them revealing a neuro-oncologic diagnosis, in two primary CNS vasculitis and in one Whipple's disease. It is important that clinicians consider AE mimics to ensure effective provisional treatment.

Dr Frederik Bartels presented "Clinical and MRI outcome predictors in paediatric anti-NMDA receptor encephalitis". First, Dr Bartels corroborates much of the neuroimaging research present throughout the day through showing that anti-NMDA receptor encephalitis is associated with significant structural and functional deficits. Dr Bartel's research demonstrates that brain volume at onset has strong predictive value of disease outcomes. For example, brain volume at onset predicts disease severity and disease course, and an abnormal MRI at onset and brain volume loss predict disease outcome.

Asst Professor Arun Venkatesan chaired the final session of the day commencing with Dr Fabiane Docagne, who presented a novel mouse model of anti-NMDAR encephalitis. Dr Docagne demonstrated that this new mouse model can reproduce the typical signs of anti-NMDAR in humans and that it is driven by B-cell mediated autoimmune responses.

Dr Melanie Ramberger, Oxford Autoimmune Neurology Group, presented her research on "Antigen-specific B- and T-cell interactions in patients with LGI1- antibody encephalitis". LgI1 (leucine-rich glioma inactivated 1) encephalitis has only recently been described and occurs when antibodies attack the LgI1 receptor. Melanie's research demonstrates that HLA antigen-specific T-cells interact with circulating B-cells, producing antibodies that target the LgI1 receptors. Describing the disease mechanisms provides potential therapeutic targets.

Phillippa Chapman of the Encephalitis Society presented their plans for the coming year. Of important note is World Encephalitis Day on February 22nd, a global awareness day organised by the Society. Further, 2019 marks their 25th anniversary which will be celebrated with a range of events and activities throughout the year as well as the launch of a new PhD fellowship and inaugural research seed-funding meaning that researchers around the world can apply for up to $10,000 per project.

Excellence in Encephalitis Healthcare awards were awarded to Dr Sylviane Defres and Hayley Hardwick, both from the Institute of Infection and Global Health, University of Liverpool. The awards recognised their work on the EncephUK study.

Best Oral presentations were awarded to Raia Blum and Amanda Tomlinson, whilst best poster presentation was awarded to Dr James Varley, Oxford Autoimmune Neurology Group, and Dr Vera Forminykh, Bujanov Moscow City Clinical Hospital.

Closing remarks were delivered by Professor Tom Solomon, and this was followed by a networking opportunity over cheese and wine. Thanks go to all the sponsors of the event: Macfarlanes LLP, the British Medical Association, Health Protection Research Unit in Emerging and Zoonotic Infections (HPRU EZI) at University of Liverpool, Public Health England in collaboration with Liverpool School of Tropical Medicine; Elysium Neurological, Routledge, PLG, the Guarantors of Brain.

If you are interested in attending Encephalitis Conference 2019 this will be held at the Royal College of Physicians, London on Monday 2nd December, 2019. You can be assured of receiving a notification of registration for the conference along with opportunities for research funding by signing up to be a professional member: https://www.encephalitis.info/professional-membership

American Epilepsy Society Meeting

Conference details: 30th November – 4th December 2019, New Orleans, USA. ***Report by:*** Mark Manford. ***Conflict of interest statement:*** None declared.

It feels that everyone is friendly in New Orleans, one of the most wonderful cities to visit and the location of this year's American Epilepsy Society meeting, but I came away with a sense of paradox. As I sat in the curiously named Fritzel's European Jazz Bar, sipping my beer and listening to a mixture of traditional jazz fused with honky-tonk and interspersed with the sophisticated banter of the band leader, on the two TV screens I could choose baseball or a commercial for a monoclonal antibody therapy. Walking a couple of hundred metres down Bourbon Street took us past young women in shorts, fishnets and tank tops in the unseasonable 5°C, which drew from a local security guard, not surprise but the normalising comment, that he was cold, so how must they feel. The jazz and gentle humour were replaced by the slightly seedy and raucous, just a short distance away. Mixed in with all of this, the French quarter, spared by hurricane Katrina in 2005, has an amazing array of art and craft and very little tourist tat, with not a franchised fast food outlet in sight.

The passion for patient care in the AES was palpable and there is maturity of patient involvement in research and treatment, with numerous publications devoted to patient centred aspects and quality of life. This is a country in which there is orders of magnitude more charitable donation to health care than in the UK. But in the same city, one could hardly walk more than fifty metres in the French quarter without encountering beggars sleeping rough. The paradox of a society where the medical needs of the disadvantaged are met, not by right, but by philanthropy; the choice of the rich whether to help the poor.

This large meeting was an excellent balance between the highly specific, covering diverse basic science and clinical topics and the broadly clinically relevant, in a number of plenary sessions. The first day opened with the role of intracranial EEG in presurgical evaluation, highlighting the sampling bias inherent to the techniques and the importance of using them in selected cases to answer specific questions, such as: "Is epilepsy arising from right or left temporal lobes?" The merits of stereotactic EEG, with its ability to detect epilepsy from the depths were compared to the broader but more superficial sampling of subdural grids, which probably also have higher complication rates. A number of speakers described roughly 50% success rates in operating on non-lesional epilepsy and, although most of these cases will need intracranial EEG, it was pointed out that not all cases will, if there is highly focal surface EEG and concordant semiology, psychology and PET scanning. The session started with a case in whom there was such poor localisation prior to electrode implantation, that it was surprising to me that it was undertaken in the first place, underlining how for some centres, MRI is not quite so dominant in decision making.

In an excellent session entitled "Epilepsy on the consult service" Scott Mintzer described the impact of enzyme inducing anti-epileptic drugs (AED) on cardiovascular health, which can be deleterious. They cause a rise in LDL cholesterol of 0.1mmol/l and independent of their own direct effect, may interfere with the cholesterol lowering effect of statins; the only one they seem not to interfere with is rosuvastatin. Moreover, they alter the metabolism of too many cardiovascular active drugs to list here, but that should be borne in mind, particularly in the older population. The knowledge of AED in pregnancy continues to expand and Page Pennell drew heavily on the latest data from the European Register for her recommendations.[1] This study states that daily doses of lamotrigine above 325mg per day have an increased risk of major malformations and that the rate with high dose lamotrigine and higher dose carbamazepine is comparable to low dose valproate ≤650mg. The safest drugs in pregnancy are low dose lamotrigine, levetiracetam and oxcarbazepine. The evidence, in combination with its more favourable pharmacokinetics is sufficient, that in my view, oxcarbazepine should displace carbamazepine in the UK from its current position in treatment of epilepsy and lamotrigine needs to be used somewhat more cautiously in women of childbearing age. The problem of drug levels in pregnancy was addressed and it is clear that as well as the known effects on lamotrigine, many other drugs are affected. A fall in AED levels to below two thirds of pre-pregnancy values is associated with a deterioration in seizure control. However, there is so much variability between women that the consensus is in favour of monitoring for most drugs where possible, including levetiracetam. In the UK, levels are not universally available.

Jeanne Young gave a dermatologist's perspective on skin rashes with AED and helpfully delineated three groups. The commonest is a mild morbilliform reaction with no systemic features and is such a common presentation, even in those not on medication, that if clinically indicated, the drug might safely be re-started to see if the rash was indeed drug related. The more serious drug rash with eosinophilia and systemic, symptoms (DRESS) and the very worrying Stevens-Johnson syndrome or toxic epidermal necrolysis necessitate stopping drugs with varying degrees of urgency. But what is the risk of a rash with another drug under those circumstances? The main paper here is old[2] but the key message is that the risk is high. Levetiracetam is relatively rash-free. And, if the patient is seizure-free, what is the risk that seizures will recur with switching to a new drug? Approximately 15% according to two studies.

There was an excellent session on epilepsy and memory. I learned how there is increasing evidence of the importance of sleep spindles, in particular fast ripple components, in linking thalamus and cortex in the formation of memory. At a molecular level BDNF expression may have a role in experimental models and DNA methylation is an important component with inhibitors adversely affecting memory. John Duncan gave an excellent review of the work using fMRI to delineate activation patterns in those with left or right mesial temporal sclerosis to predict the cognitive outcome of epilepsy surgery,[3] but there are still centres using the Wada test, which also featured in a couple of posters.

Sudden unexplained death in epilepsy (SUDEP) has been a focus for over twenty years but research has been largely descriptive. Earlier studies suggested it was less common in children but a more methodologically robust study from Sweden refutes that view.[4] Three main mechanisms have been postulated; arrhythmias, apnoea and suppression of brain electrical activity. In sessions devoted to this topic, hypotheses underlying these mechanisms were described. They include 5-HT3 and 5-HT4 receptors implicated in a mouse model of fatal apnoea, which are altered by existing medications

acting on these systems; hypoperfusion of the brain blocked by COX-2 inhibitors and genetic abnormalities with overlap with long Q-T syndrome. It is increasingly recognised that patients with these cardiac channelopathies may also suffer seizures, which had previously been attributed to syncope but provide a means for understanding interaction between seizures and cardiac events which may be fatal. Whilst heart rate and regularity are easy to measure in seizures, vascular reactivity and alterations in blood pressure are not and may be another relevant mechanism, again amenable to existing medications. Suppression of brain activity seems to be more likely in patients with seizures with a longer tonic phase, providing a potential means of predicting who may be more at risk.

This leads on to the question of seizure detection and prediction. A number of commercially available devices are postulated to identify when patients are experiencing a seizure. They are based on a range of technologies, including accelerometry, HR changes and changes in skin conductance. None is yet particularly reliable but one has been licensed by the FDA. In a fascinating session, Robert Fisher speculated where epilepsy would be in the next ten years. He predicted that it would be the decade of AI, with this being applied to seizure detection devices; to diagnostic algorithms and to treatment algorithms for patients with epilepsy. He predicted that clinicians would mostly be needed for the more global decisions, education and patient interaction. I am not sure if I am pleased or not that I shall not be practising to see it.

Cannabidiol (CBD) is the drug of the moment, although only licensed for Dravet's and Lennox Gastaut syndromes. Tyler Gaston guided us through the differences between pharmaceutical CBD (pharmacologically consistent) and artisanal cannabis products (highly inconsistent). In terms of efficacy, CBD really is very little different from other drugs that have been trialled and there is less fanfare around fenfluramine in LGS, which is just as effective. CBD's anti-epileptic activity appears to be at a range of sites unrelated to the cannabinoid receptor. Life would be so much easier if it were just called something else!

A session on febrile status epilepticus described how the FEBSTAT study[5] has shown that prolonged febrile seizures are associated with hippocampal sclerosis, although the relationship appears complicated, for example more on the right than the left. This provides an opportunity to intervene to prevent epilepsy and work on mechanisms has identified the potential importance of interleukins and neuronal restrictive silencing factor, which are potentially mediated through alterations in micro RNA's. A possible early marker of risk is increased T2* signal in the hippocampus, a sequence not standard in epilepsy protocols, but it might become so, if an intervention were possible.

Finally, no conference would be complete without some genetics. One of my practical enigmas is in how many of my patients with refractory epilepsy since childhood who are in my adult clinic, and who have normal imaging and no clear reason for their epilepsy, should I be requesting genetic testing? The answer is apparently all of them. I am not sure Matthew Hancock or particularly Philip Hammond would agree. Still, I prefer working in healthcare where access is relatively uniform even if that may not always match the very best in some less equal systems.

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David Marsden Movement Disorders Symposium

Conference details: 19th November, 2018, London, UK. ***Report by:*** Amit Batla. ***Conflict of interest statement:*** None declared.

For those who did not know David Marsden, he was one of the most highly cited neuroscientists of the 20th Century. He worked for 17 years as an academic neurologist at King's College Hospital (KCH) and the Institute of Psychiatry (IoP) in Denmark Hill, and then for 11 years at the National Hospital for Neurology and Neurosurgery at Queen Square. Although he died young, he remains one of the most influential people in the field of movement disorders and neurology.

Most of his work related to Parkinson's disease (PD), dystonia, tremor, myoclonus and other movement disorders. To mark 20 years since his death, and 80 years since he was born, a half-day movement disorders symposium was organised at the Athenaeum club in Pall Mall.

The symposium was attended by movement disorder specialists from across the world, plus David's former wife and four of his daughters. It featured ten talks delivered by ex-fellows from King's or Queen Square, or both, all of whom hold senior Professorships. Mark Hallett, Peter Jenner, Jose Obeso, Tony Lang, John Rothwell, Brian Day, Niall Quinn, Marjan Jahanshahi, Kailash Bhatia and Andrew Lees presented an excellent perspective of their own experience of working with David. It was most interesting to see how they carried forward the ideas of that time, and how things changed over the years that followed their fellowship days, or with their time spent with him at Queen Square.

Ray Chaudhuri, representing David's legacy at King's, chaired a session, and Brian Day gave the audience a perspective (in places hilarious) of working with David during his

tenure at KCH and IoP. David also worked very closely with Stanley Fahn in New York, and with him set up the International Movement Disorder Society and Movement Disorders Journal. Although Stan could not attend in person, he sent a very warm and personal video appreciation.

All of the speakers are well known for their own work in movement disorders, and their talks were very informative for trainees, fellows, and young consultants like me. While the speakers began the session by remembering the time they spent with David, it was most interesting to see the transformation of the field over the years. David started his career by better defining the symptomatology and pathophysiology of movement disorders, and developed techniques of diagnosis and treatment. Over his life, and following his heritage, David and his fellows have been instrumental in investigating all aspects of movement disorders. Some of the talks were focused on specific areas of David's work in PD, corticobasal syndrome, dystonia, myoclonus and tremor. Others covered current but related aspects of their research, such as dementia, and Prof Olle Lindvall from Sweden sent an appreciation of David's pivotal role in developing his pioneering work in foetal nigral cell grafts. The day ended with a clinical video presentation revealing genetic diagnoses of some of David's patients who were undiagnosed in his life, but later revealed by advances in neurogenetics.

The evening ended with a champagne reception which reminded everyone of David's love for good wines and his spirit of joy. Everyone raised a glass to toast David's work and legacy, and his family.

In our rapidly changing world of science, the symposium reminded us of the permanent influence on the field of neurology and movement disorders that David Marsden has left us.

Swansea University & Elysium Neurological 'Neurobehavioural Disability after Acquired Brain Injury: Recent Innovations in Clinical Practice and Delivery' conference

Conference Details: 26 November 2018, Swansea, UK. ***Report By:*** Eleanor Bryant, Aimee Pink & Dr Claire Williams, Department of Psychology, College of Human and Health Sciences, Swansea University. ***Conflict of Interest statement:*** None declared.

The conference brought together leading experts in acquired brain injury (ABI) to present the latest innovations in clinical practice and delivery, attracting a range of exhibitors and a diverse mix of delegates interested in and/or involved in the care of individuals with ABI. The conference provided an excellent learning environment for delegates to support their continuing professional development, with plenty of opportunities for questions and networking.

Professor Nick Alderman (Clinical Director, Neuropsychological Rehabilitation Services, Elysium Healthcare) commenced proceedings by reviewing how self-monitoring training (SMT) can be an effective strategy for individuals considered 'treatment resistant' to standard rehabilitation techniques. Following a model based on 'response-cost' delivered in an inpatient setting, he proceeded to outline a practical programme involving SMT, reinforcement and goal setting that could be utilised in the community. Positive reductions in target behaviours were demonstrated through a series of case studies, with gains showing both longevity and generalisability.

Dr Jessica Fish (Clinical Psychologist, St George's University Hospitals NHS Foundation Trust) took the stage next to discuss the rehabilitation of confabulation following ABI, sharing the journey of a brain injury survivor as they struggled to separate their dreams from reality. Dr Fish presented an informative and detailed overview of potential rehabilitative strategies for confabulation, emphasising the importance of not directly challenging the individual but helping them to independently identify reality versus confabulated information. Dr Fish also shared her progress with a systematic review of treatment for confabulation and encouraged continued sharing of best practice to support rehabilitation efforts.

The next speaker was Louise Smith (Hospital Director, Elysium Neurological) who shared her experiences and observations of being a manager in a neurobehavioural setting, along with its triumphs and challenges. Specifically, she explored the pitfalls of multidisciplinary team working, presenting a 'Transdisciplinary Team' (TDT) approach as an alternative. She explained how TDT working requires 'buy-in' from all disciplines that are all jointly responsible for delivering services to clients, comprehensive training, effective induction procedures for new staff, and the creation of a shared ethos. Whilst resource intensive and not without challenges, she explained how

the TDT approach is ultimately structured around making the client the centre of service delivery – a message wholly welcomed by all in attendance.

Dr Giles Yeates (Clinical Neuropsychologist and Tai Ji instructor, Neuro Flow www.neuro-flowgroup.com) presented an engaging and interactive session on the inclusion of Tai Ji in rehabilitation, with delegate's practising cloud hands and observing impressive demonstrations. He explained how traditional talking therapies may not be suitable for everyone, advocating for a mind-body approach as an alternative. The importance of experiential experiences, flow states and liminal experiences were discussed, as well as the evidence base for the benefits of Tai Ji for achieving simultaneous physical and psychological gains in complex health conditions. Following his presentation, many delegates expressed the desire to incorporate such approaches into their work.

After lunch, Dr Mark Holloway (Brain Injury Case Manager, Headfirst) presented 'Case Managing the Environmentally Governed in the Ungovernable Environment of the Community'. Drawing on his extensive experience, Dr Holloway provided a compelling and honest account of the everyday challenges that accompanies such work. Illustrated via a series of case studies, he explained how the community is not a locked environment (and never will be), how case management is based in the "messy reality of society, family and home", and how there are multiple service (e.g., a naively applied social model of disability), practical (e.g., fluid and fast moving environment; staff needs) and human (e.g., burn-out; conflicting needs of parties) barriers to successful community management. Dr Holloway concluded his talk by reviewing what case management looks like when it works, emphasising the importance of having a supportive team (absence of blame, presence of care) with a responsive, flexible and common goal, strong leadership, the ability to 'ride the storm' whilst being prepared to act decisively if risks or the environment is unmanageable, and recognising and valuing the role of support workers who are on the ground dealing with complex challenges on a daily basis.

The next speaker was Dr Richard Maddicks (Consultant Clinical Neuropsychologist, Psychology Chartered) who discussed why relationships matter in neurorehabilitation. His engaging talk emphasised how social isolation can be the most profound life change for people following ABI. He proceeded to explore a range of topics, including how the decision-making process can be a binding activity, family member's appraisal of stress, the core components of interpersonal therapy, and relationship stability and quality after ABI. Dr Maddicks also highlighted the importance of bringing together the knowledge and experience of clinicians **and** family members, as well as presenting a manifesto for 'putting the social into rehabilitation'.

The conference was drawn to a close by Joanna Humphreys (Music Therapist, Nordoff Robbins) who could not resist the opportunity to make some music – delegates made a fine choir with impressive body percussion skills! She proceeded to present a moving case study of an ABI survivor's journey through music therapy, illustrating how they channelled their emotions through music, highlighting the anger and bitterness felt in contrast with the certainty, beauty and safety of music. As a result, there was not a dry eye in the house.

Save the Date: Next year's conference will take place on 25 November 2019, Swansea UK. Further details will be announced early 2019.

West of England Seminars in Advanced Neurology (WESAN)

Conference details: 22nd-23rd November 2018, Exeter, UK. ***Report by:*** Dr Ibrahim Imam, Consultant Neurologist, Royal Devon and Exeter Hospital.
Conflict of interest statement: None declared.

The West of England Seminars in Advanced Neurology (WESAN) is held annually in Exeter. Each year 13 invited speakers talk on practical and topical neurological issues, and the delegates consist of neurology trainees and consultants.

The first talk this year, 'My approach to diagnosing tremor in clinic', was presented by Jane Alty, Consultant Neurologist at Leeds Teaching Hospitals NHS Trust. She presented interesting videos of tremor syndromes, including isolated shaving tremor and snooker-player tremor. She showed the differences between ET and a re-emergent postural tremor of Parkinson's disease (PD). She highlighted features of dystonic tremor such as isolated head tremor, thumb tremor, and focal muscle hypertrophy. She also explored the diverse differential diagnoses of tremor.

'The spectrum of IgG4 antibody disorders in neurology' was the title of the presentation by Burden Professor of Neurology, Neil Scolding. He presented the case of a construction worker who developed diverse neurological features including multiple cranial neuropathies. He reviewed the characteristic features which are hypertrophic pachymeningitis, hypophysitis, and orbital involvement. He also reviewed its other manifestations such as retroperitoneal fibrosis, pancreatitis, interstitial lung disease, and Reidel's thyroiditis. He pointed out that IgG4 antibodies are also detected in NF155 CIDP, anti-MUSK myasthenia gravis, and LGI1 limbic encephalitis.

Jasper Morrow, Consultant Neurologist at the National Hospital for Neurology and Neurosurgery presented 'The role of MRI in muscle disorders'. He discussed the uses of MRI such as in confirming diagnoses, guiding the site of biopsy, and directing genetic testing. He presented illustrative cases such as bilateral trapezius muscle atrophy in FSHD, central gastrocnemius muscle stripe in myotonia congenita, and islands of preserved muscle in BICD2 gene mutation. He reviewed the utility of MRI in monitoring disease progression and in assessing response to treatment.

The fourth talk, 'Innovations in brain tumour management', was presented by Katia Cikurel, Consultant Neurologist at King's College Hospital. She reviewed recent advances in brain tumour treatment such as the fluorescent dye, gliolan, intensity modulated radiotherapy, the benefits of awake craniotomy, the use of intra operative monitoring. She discussed the significance of MGMT methylation status, IDH and ATRX positivity. She reviewed the indications and benefits of early intervention with radiotherapy and chemotherapy for low grade gliomas, and of radiotherapy in controlling resistant seizures.

Howard Faulkner, Consultant Neurologist at Bristol, presented on 'Epilepsy surgery: when and why?' He pointed out that the 33% rate of drug-resistant epilepsy has not changed despite the use of new AEDs. He said epilepsy surgery is beneficial in both lesional and non-lesional epilepsy. He discussed the patient selection protocol for surgery. He noted the importance of video-EEG in confirming diagnosis and refuting misdiagnoses such as functional seizures and cardiogenic disorders. He discussed the use of SPECT scans to localise the seizure onset in non-lesional cases, and invasive EEG techniques, using depth electrodes and robotic stereo EEG, to establish surgical targets.

'Neuropsychiatry and the borderzone with neurology' was the title of the talk by Andrea Cavanna, Consultant in Behavioural Neurology at the National Centre for Mental Health, Birmingham. He reviewed the neuroanatomical substrates of behavioural neurology, making references to leading figures in the field. He explored the relationship between consciousness and neurological disorders such as epilepsy. He discussed the emotional manifestations of seizures and the psychiatric comorbidities of epilepsy. He reviewed the behavioural spectrum of Tourette's syndrome such as OCD, ADHD, and affect dysregulation.

The title of the talk by Pooja Dassan, Consultant Neurologist at Imperial College Healthcare Trust, was 'A practical approach to neurological problems in pregnancy'. She reviewed migraine, the most frequent cause of headache in pregnancy. She discussed other causes of headache in pregnancy such RCVS, PRES, IIH and cerebral vein thrombosis. She reviewed the safety of headache medications in pregnancy, and the preconception and intrapartum management of epilepsy. She discussed the management of MS in pregnancy with emphasis on the safety of imaging and of disease modifying treatments (DMTs).

The title of the talk by Sybil Stacpoole, Consultant Neurologist at Peterborough and Addenbrooke's Hospitals, was 'Resolving the diagnostic and management dilemmas in multiple sclerosis'. She reviewed the diagnostic criteria for multiple sclerosis and discussed paroxysmal symptoms and relapses. She reviewed the NHS England treatment algorithm, and discussed risk stratification data indicating that brain stem lesions, multiple lesions, and contrast enhancement portend a poor outcome. She discussed the monitoring protocols for the different DMTs, and the uncertainties surrounding stopping treatment.

Alexander Rossor, Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, presented 'My approach to the hereditary neuropathies'. He described the classical presentation of demyelinating CMT, and reviewed the axonal hereditary neuropathies, noting that MFN2 and MORC2 are the commonest genetic mutations of CMT2. He discussed the split hand muscle atrophy of CMTX, and vocal cord palsy in CMT1D. He discussed gene panel testing for hereditary neuropathy, and reviewed the management and emerging treatments of HNPP and familial amyloid polyneuropathy.

'How I manage the patient with difficult idiopathic intracranial hypertension' was the title of the presentation by Alexandra Sinclair who runs the IIH service at University Hospital, Birmingham. She reviewed the pathogenesis and clinical features of IIH in the context of the latest guidelines. She discussed the diagnostic pitfalls of IIH, and reviewed its medical management. She discussed CSF diversion procedures which are required in about 8% of cases to prevent visual loss. She discussed the utility of neurovascular stenting, and emerging drug treatments such as 11beta HSD1 inhibitors and GLP-1receptor agonists.

Anne Rosser, Professor of Clinical Neuroscience at Cardiff University, presented several videos to illustrate her talk, 'Huntington's disease: spectrum and treatment prospects'. She reviewed the motor, cognitive, behavioural, and psychiatric features of HD, noting that cognitive impairment is a better predictor of dependence than motor features. She discussed the treatment of HD, explaining the move away from treating chorea unless it is severe or disabling. She highlighted the importance of physical therapy, and she reviewed the emerging therapies of HD including gene silencing and cell replacement therapy.

Charlotte Dawson, Consultant in Metabolic Medicine at Queen Elizabeth Hospital Birmingham, presented on 'Acute neurological presentations of inherited metabolic disorders'. She illustrated her talk with cases such as OTC deficiency presenting with hyperammonaemic encephalopathy. She discussed Fabry disease and recommended testing in people with a family or personal history of unexplained cardiomyopathy and/or renal disease. She discussed CPT2 deficiency and McArdle's disease as the commonest adult causes of metabolic myopathy, often presenting with rhabdomyolysis.

The last talk of the course was presented by Jenny Vaughan, Consultant Neurologist at Imperial College Healthcare Trust, and it was titled 'Call the neurologist! Delivering doctors from lawyers in 21st century Britain'. Her presentation was on the investigation of doctors for the crime of gross negligence manslaughter (GNM). She discussed her personal involvement in the prosecution and eventual successful appeal of surgeon David Sellu, and paediatrics trainee Hadiza Bawa-Garba. She explored the factors that contributed to their convictions, and the systemic and human factors that cause tragic healthcare-related deaths.

WESAN 2019 is scheduled to be held on 21-22 November 2019. For updates, please check the WESAN website www.wesan.org.uk
A more extensive version of this report is available on our website: https://bit.ly/2SbEQ1F

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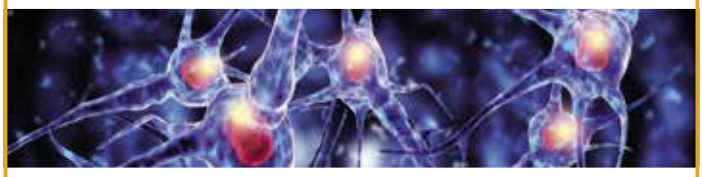

The British Neuro-Oncology Society Annual Meeting is taking place in the Queen Elizabeth II Centre, London on the 3rd to 5th July 2019.

The meeting ensures that all those working in neuro-oncology in the UK meet to learn, discuss and impart findings within a friendly and informative atmosphere.

This three-day multidisciplinary educational event incorporates plenary sessions, presentations, debates, and prize categories across various neuro-oncology fields; and will for the first time this year also play host to both the Glioma Club and Bootcamp (Wednesday 3 July).

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IMPORTANT DATES

Call for Abstracts Deadline Closes - 22 March 2019
Early Bird Registration Closes - 6 May 2019

For further details regarding confirmed speaker's, the conference programme and / or to register to attend please visit

www.bnos2019.com

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Taking the first steps in ending service variance for MS

Conference details: 1-2 November, Birmingham, UK. ***Report by:*** Charlotte Peel, MS Academy.
Conflict of interest statement: None declared.

On 1st and 2nd November, a gathering of health care professionals, service providers, charities and planners came together to hear eminent individuals presenting the current challenges in, and barriers to, delivering equitable and optimal care for people living with multiple sclerosis (MS).

During the course of the two day meeting, the way forward to ending variance in MS services was broken down into three core pathways: patient empowerment and activation, data collation and interpretation, and education across both professional and patient communities.

Challenging presentations questioned everything from implementation of the NHS England 'treatment algorithm for MS disease-modifying therapies' (DMTs), to whether the expanded disability status scale (EDSS) is the best marker for measuring disease progression in terms of data gathering, to what constitutes an empowered patient and how the professional community can better enable this. The room was tasked with questioning, dissecting and debating each topic in relation to MS support, looking to decrease variation and optimise services for those living with the neurological condition.

One of the biggest take-home messages was that 'change starts with us' in clinical practice, summed up succinctly by Jerry Clough of OPTUM, who began his address to the room with 'You are the apex of this service'. Highlighting that to wait for commissioners or service planners to instigate dramatic and lasting change is not the answer, he was one of many voices calling for change from within professional practice itself.

Similarly essential and impactful was the need to empower people with MS, or 'MSers' as the community refer to themselves, to self-manage and lead on their own condition and care, and to be equal partners in the design of MS services and support. George Pepper, MSer and founder of ShiftMS closed his keynote speech with the challenge: 'We must engage the more passive MSers to be more active in managing their own condition'.

The level of work to be done is vast, and yet in breaking it down into each individual's service delivery, patient interactions and chosen fields of research, real progress can be made now. Core areas of work have already begun to make headway, and professionals and people with MS alike can begin to get involved in the movement to reduce variance now.

Rachel Dorsey-Campbell, neuroscience pharmacist at the Imperial NHS Trust, presented on a project she and colleagues have already begun in breaking down the monitoring essential to safe delivery of DMTs and calculating the associated - and as yet, unmet - costs. Rachel presented initial data finding that, with over 20,000 patients on a DMT, the cost in blood tests alone is in excess of £350,000 each year. Taking into account the cost in time to a specialist nurse or pharmacist - a time burden calculated at over 26 hours per month - and the annual, currently uncommissioned, cost in staff time could be as much as £1.2 million.

This key project is just one of many strands of work beginning to unpick the problems to better inform the solutions, and alongside podcasts of all the presentations given at this event, is available on our website. We invite you to join our community, dedicated to ending variance in MS services and support, and get actively involved; you can follow the progression on Twitter by searching #MSVariance and learn more about opportunities to join bodies of existing work on our website.

To find out more specifically about the DMT monitoring project, listen to Rachel's full presentation and read a more in-depth coverage of the project to date, at www.multiplesclerosisacademy.org or contribute to the project here https://multiplesclerosisacademy.org/resources/commissioning/dmt-monitoring-time-and-cost-burden/

Christchurch Group announces appointment of Donald Muir as Non-Executive Chairman

Christchurch Group, operator of specialist neurological rehabilitation, has recently announced the appointment of Donald Muir as Non-Executive Chairman.

With over 25 years' experience of managing positive business transformation in the telecoms and technology and healthcare sectors, Donald's knowledge will be an asset to the organisation.

Notably in healthcare, Donald led the operational transformation of three NHS Trusts, resulting in substantial improvement in performance, care quality and patient satisfaction.

Prior to his appointment at Christchurch Group, Donald was Non-Executive Director of Cambian plc, provider of children's care services and autism schools, delivering improvements in operational performance and quality of care.

Richard Mckenzie, CEO of Christchurch Group, added: "Donald's experience will be invaluable to our organisation and we are looking forward to working with him to further develop the business and continually improve on the quality of service we are able to provide to our patients."

Donald added: "I'm excited about joining the Christchurch team. In my role I will be dedicated to supporting the group in succeeding with their vision to be the leader of neurological rehabilitation in the healthcare sector."

Donald's focus will be to work closely with the executive team to enhance capabilities and outputs, with the key focus being on the continued high quality of care delivery and ensuring full occupancy of the facilities.

Christchurch Group was established in 1998 to provide high quality brain injury rehabilitation within a community setting. The organisation has since grown into a leading provider of specialist neurological rehabilitation that offers a range of specialist services across eight centres in York, Lincoln, Birmingham, Northampton, Bedford and Harwell in Oxfordshire.

https://www.christchurchgroup.co.uk

ACNR announces new partnership with Taylor & Francis

Routledge and CRC Press - part of Taylor & Francis Group - publish a wide range of books within the fields of Behavioural Science and Medicine. This contains a large collection of Neurology and Neuropsychology books including a number of dedicated series. They work with leading authors in their fields to bring the latest research and professional methods to the forefront in their books.

The aim of this reciprocal partnership is to support ACNR's readers by offering a range of benefits such as 20% discount on all books purchased via Routledge or CRC Press, free content resources, prize draws and much more to come. We envisage this as a long and fruitful partnership that delivers exclusive benefits to our readers.

To find out more, visit https://bit.ly/2EQKvpT

New Rehabilitation Prescription now available

A new Rehabilitation Prescription (RP2019), the tool that documents the rehabilitation needs of the individual with Acquired Brain Injury (ABI), is now available, with versions available for adults and children.

Professor Chris Moran, National Clinical Director for Trauma to NHS England, and Professor of Orthopaedic Trauma Surgery at Nottingham University Hospital said: "Neurorehabilitation is a key component of the major trauma network; an essential part of good trauma care and good patient outcomes. Rehabilitation needs should be assessed shortly after a patient is admitted to the major trauma centre, delivered during the inpatient phase, and continued in a trauma unit or in the local community.

ABI ALLIANCE
putting brain injury on the map

This new RP details the neurorehabilitation needs of both children and adults, and in order to maintain the continuity of rehabilitation, a copy should be given to both the patient and/or family as well as their GP."

Professor Michael Barnes, ABI Alliance Chair said: "The Acquired Brain Injury Alliance is a collaborative venture between charities, professional groups and industry coalitions working in the field of ABI. We are supporting the availability of this revised version of the RP to emphasise its key role in ensuring patients access neurorehabilitation services following discharge.

Read more at https://bit.ly/2HtddPU

2.5 million genomic research programme

A collaboration between UK charity the Epilepsy Society, and Belgian biopharmaceutical company, UCB, could bring life-changing treatments to people with epilepsy whose seizures do not respond to current treatments.

A €2.5 million genomics research programme being launched by the UK-Belgium partnership offers greater hope than ever of a more personalised, targeted approach to diagnosis and treatment based on each person's unique genetic make-up.

Scientists expect that their research could result in improved, better focused treatments for people with epilepsy, potentially leading to a life free from seizures.

And they believe that the collaboration's global positioning has the potential to bring new treatments on a world-wide scale to people whose epilepsy is currently difficult to treat.

What makes the Epilepsy Society/UCB collaboration unique is the detailed clinical data that it is able to harness. Epilepsy Society's Chalfont Centre in Buckinghamshire provides tertiary care for people with the most severe and uncontrolled epilepsy. Its integrated medical care and clinical research presents an unparalleled opportunity to progress knowledge and understanding.

The long-term aim of the partnership will be to use key insights from research to design and develop improved, personalised approaches to the management of epilepsy, tailoring it to individual needs and genetic characteristics.

Professor Sanjay Sisodiya, Professor of Neurology at UCL and the Epilepsy Society's Director of Genomics, who is leading the research partnership within the charity said: "Advances in genomics present exciting potential for a paradigm shift in epilepsy. We hope to use them to gain a much better understanding of the disease trajectory, improving diagnosis and treatment for people living with epilepsy. Our hope is that by embracing genomics we will be able to provide personalised care for people with epilepsy, eventually helping us to identify the right treatment, first time."

MERCK

Welcome to MAVENCLAD®

(CLADRIBINE 10 MG TABLETS)

AN INNOVATIVELY SIMPLE* APPROACH FOR ADULTS WITH HIGHLY ACTIVE RELAPSING MULTIPLE SCLEROSIS (MS)

ONLY MAVENCLAD® CAN DELIVER AND SUSTAIN UP TO 4 YEARS OF DISEASE CONTROL WITH A MAXIMUM OF 20 DAYS OF ORAL DOSING IN THE FIRST 2 YEARS[1–4]

www.mavenclad.co.uk

*Maximum of 20 days of oral dosing in the first 2 years with no further treatment required in the next 2 years

REFERENCES: 1. MAVENCLAD® Summary of Product Characteristics. Merck; **2.** Giovannoni G, *et al. N Engl J Med* 2010;362:416–426; **3.** Giovannoni G, *et al. N Engl J Med* 2010;362:416–426 (supplementary information); **4.** Giovannoni G, *et al. Mult Scler.* 2017;doi:10.1177/1352458517727603.

PRESCRIBING INFORMATION – UK AND IRELAND
MAVENCLAD® cladribine (Please refer to the full Summary of Product Characteristics before prescribing)
PRESENTATION: Cartons of 1, 4 or 6 tablets. Each tablet contains 10 mg of cladribine. **INDICATIONS:** Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. **DOSAGE AND ADMINISTRATION:** Must be initiated and supervised by a physician experienced in MS treatment. Recommended cumulative dose: 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year. Each course comprises 2 treatment weeks, one at the start of the first month and one at the start of the second month of each year. Each treatment week comprises 4 or 5 days on which the patient receives 10 mg or 20 mg as a single daily dose, depending on body weight. For details, see dosage tables in the SPC. No further cladribine treatment is required in years 3 and 4. **CONTRAINDICATIONS:** Hypersensitivity to cladribine or to the excipients; HIV infection; active chronic infection (tuberculosis or hepatitis); initiation in immunocompromised patients including those receiving immunosuppressive or myelosuppressive therapy; active malignancy; moderate or severe renal impairment (creatinine clearance <60 mL/min); pregnancy and breast-feeding. **PRECAUTIONS:** Not recommended in moderate or severe hepatic impairment. Exercise caution in elderly patients. Determine lymphocyte counts before initiation in years 1 and 2, 2 and 6 months after treatment start in each treatment year. Count should be normal pre-treatment in year 1. If count below 500 cells/mm^3 at 2 or 6 months, actively monitor until values increase. If count below 800 cells/mm^3 pretreatment in year 2, delay treatment. Stop treatment if recovery takes more than 6 months. Screen for latent infections prior to initiation in years 1 and 2. Delay initiation in latent or acute infection until treated. Varicella zoster vaccination is recommended in antibody-negative patients prior to treatment initiation. Delay initiation for 4-6 weeks following vaccination. Consider anti-herpes prophylaxis during grade 4 lymphopenia. If lymphocyte count falls below 500 cells/mm^3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt or delay MAVENCLAD until infection has resolved. Perform baseline MRI before initiating MAVENCLAD (usually within 3 months). Evaluate benefit-risk prior to initiation in patients with previous malignancy. Advise patients to follow standard cancer screening guidelines. Exclude pregnancy before initiation in years 1 and 2. Before initiation in year 1 and 2, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used by both male and female patients during treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraception should add barrier method during treatment and for at least 4 weeks after last dose in each treatment year. In patients previously treated with immunomodulatory or immunosuppressive products, consider their mode of action and duration of effect before initiation of MAVENCLAD. Consider an additive effect on the immune system when such products are used after treatment with MAVENCLAD. When switching from another MS agent, perform a baseline MRI. In patients requiring blood transfusion, irradiation of cellular blood components is recommended prior to administration. Not to be taken by patients with hereditary fructose intolerance. Separate administration of any other oral medicinal product by at least three hours from MAVENCLAD administration. Concomitant treatment with other disease-modifying treatments for MS not recommended. Monitor haematological parameters when taken with other substances that affect the haematological profile. Do not initiate treatment within 4-6 weeks of live or attenuated live vaccines. Avoid vaccines during and after treatment while white blood cells not within normal limits. Avoid co-administration of ENT1, CNT3 or BCRP inhibitors during the 4-5 day treatment period. Consider possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered. **SIDE EFFECTS: Very common**: Lymphopenia **Common**: Oral herpes, dermatomal herpes zoster, decreased neutrophils, rash, alopecia **Other side effects**: Tuberculosis. In clinical studies and long-term follow-up, malignancies were observed more frequently in cladribine-treated patients compared to placebo. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **LEGAL CATEGORY:** POM. **PRICE:** Pack of 1 tablet: £2,047.24 Pack of 4 tablets: £8,188.97 Pack of 6 tablets: £12,283.46 For prices in Ireland, consult distributor Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands; EU/1/17/1212/001, 002 & 004 **For further information contact: UK:** Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono (Ireland) Limited, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590. **Date of Preparation:** August 2018 **Job No**: UK&IE/CLA/0818/0089

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. In the Republic of Ireland information can be found at www.hpra.ie. Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckgroup.com.

Job No: UK&IE/CLA/0817/0072k(1) Date of preparation: October 2018

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