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TO 4 YEARS OF DISEASE CONTROL WITH A MAXIMUM OF 20 DAYS’ ORAL TREATMENT1–5

at the start of the second month of each year. Each treatment week comprises 4

2.\8\9\2 years, administered as one treatment course of 1.75 mg/kg per year. Each

Determine lymphocyte counts before initiation in years 1 and 2, 2 and 6 months

PRECAUTIONS:

**INDICATIONS:**

Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

**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:**

Hyperreactivity to cladribine or to the excipients; HIV infection; active chronic infection (tuberculosis or hepatitis); initiation in immunosuppressed patients including those receiving immunosuppressive or myelosuppressive therapy; active malignancy; moderate or severe renal impairment (creatinine clearance <40 ml/min); pregnancy and breast-feeding. PRECAUTIONS: Not recommended in moderate or severe hepatic impairment. Exercise caution in elderly patients. Deteriorate 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/mm3 at 2 or 6 months, actively monitor until values increase. If count below 800 cells/mm3 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/mm3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt or delay MAVENCLAD until infection has resolved. Perform baseline MRI within 3 months of MAVENCLAD initiation. 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, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used during treatment and for at least 6 months after the last dose. Women using 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. 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 EMT, ONT or BCR 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


Marketing Authorisation Holder and Numbers: Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands; EU/1/1/1212/001, 002 & 004 For further information contact: UK: Merck Serono Ltd, Reffatt Cros, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. Republic of Ireland: Merck Serono (Ireland) Limited, 4045 Kingswood Road, Clonsha Business Campus, Dublin 24. Tel: 01 6683990. Date of Preparation: July 2018

Job No: UK/AE/CLA/00718/00169
Many congratulations to Charlotte Stagg Stagg, University of Oxford, (pictured) who has been made a Professor of Human Neurophysiology.

Congratulations also go to Mark Hallet and Alastair Compton who have both received EAN honorary membership awards. Professor Compton received his award for this exceptional work in multiple sclerosis and Professor Mark Hallett for his outstanding work on human motor control and its disorders.

Chroma are CMSUK Finalists for Neurologic Music Therapy

Chroma’s Neurologic Music Therapy service, widely commissioned by case managers and solicitors alike, has been chosen by CMSUK as a finalist in the “Rehabilitation Innovation of the Year” category, as part of their annual awards.

For more information see www.wearechroma.com

Neuropsychologist Sallie Baxendale wins international award

Epilepsy Society’s neuropsychologist Sallie Baxendale has scooped a prestigious international award for the significant difference she has made to the treatment and care of people with epilepsy.

Sallie has been awarded the 2018 International Neuropsychological Society (INS) Arthur Benton Mid-Career Award which is only presented once every seven years to one person worldwide for their scientific achievement.

Sallie said: "I am particularly pleased to receive this award as it is the first time that it has been given in the field of epilepsy. Epilepsy doesn’t usually get that much attention so it is a real accolade to see the INS recognise the contribution of people with epilepsy in the clinical research of brain behaviour."

Sallie has had over 140 academic papers published. She was nominated for her work spanning more than 20 years including research in temporal lobe epilepsy; championing functional magnetic resonance imaging in the assessment of language and memory; and the development of clinical algorithms which enable accurate prediction of post-surgery memory performance and help to inform decision making for those considering epilepsy-surgery.

For more information contact: nicola.swanborough@epilepsysociety.org.uk

Deadline for UKABIF Film Award entries

The deadline of 28th September is fast approaching for the United Kingdom Acquired Brain Injury Forum (UKABIF) Film Award 2018, sponsored by Elysium Neurological.

UKABIF’s Film Award will acknowledge, recognise and reward a short film, of no more than 30 seconds duration, that enhances the understanding of ABI. UKABIF is inviting submissions that mirror its key priorities i.e. neurorehabilitation in hospital and/or in the community, or about brain injury in the context of school, prison or sport.

For further information and details on how to enter please visit: www.ukabif.org.uk/filaward
This issue comes after a long, hot summer, with the NHS entering its 70th year. Returning to thoughts of the beginning of a new term and looking towards the end of the year, we have some clear guidance on a common disease which is constantly refining its criteria and management. The management of atrial fibrillation in stroke prevention is reviewed succinctly by eminent stroke neurologist Dr Bhavini Patel.

Harsha Narayanamurthy, Peter Whitfield and Katheena Kurian (Bristol and Plymouth) again distil the 2016 World Health Organisation classification of brain tumours in a second article – this time focusing on paediatric tumours.

Dr John Pearce highlights the lesser known Rufus of Ephesus, an early pioneer of medicine who first named diastole and systole among many other achievements.

Natalie Birch and colleagues describe an unusual cause of carpal tunnel syndrome in our case report, and Andrew Larmer outlines cases of Render’s syndrome from literature in our regular Neurology Literature feature.

We cover conferences, book reviews and offer opinion pieces from writer Kate Swindlehurst who movingly describes the experience of Parkinson’s and the Tango Effect, as well as a further piece on cannabis oil, which is one clinician’s view of the current status of this compound.

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Ann Donnelly, Co-Editor

Email. Rachael@acnr.co.uk

Erratum
In the May-July 2018 issue of ACNR, incorrect figures 15, 16 and 17 were published in The 2016 WHO Classification of adult CNS tumours – the essentials: Part 1. The article on our website at www.acnr.co.uk is correct, and you can download a corrected PDF from https://bit.ly/2Nrvhtd
The 2016 WHO Classification of paediatric CNS tumours – the essentials – part 2

Abstract
Brain tumour classification is critical for understanding the behaviour of tumours. The WHO classification of CNS tumours has been among the best resources for the latest knowledge about tumours of the nervous system. New to the 2016 classification are concepts of ‘layered diagnosis’ and ‘integrated diagnosis’ which are a combination of traditional histological grading with molecular genetics. It is important that clinicians understand the basic concepts and important differences from the earlier versions for their daily practice.

Introduction
Classification of the different brain tumours has been one of the primary means of understanding them by organising them according to their various characteristics. Rudolf Virchow’s report on brain tumour classification in 1863 was the first known attempt at classifying brain tumours. From then, through the seminal papers of Bailey and Cushing in 1926 explaining the potential relations between the developing brain and brain tumours, to the concept of tumour grading introduced in 1949 by James Kernohan and colleagues, there have been many significant contributions in this field. Zulch et al., published the first WHO based classification in 1979, followed by the second (1993), third (2000) and fourth (2007) editions. A briefly popular alternative tumour grading system called the St Anne – Mayo grading system was also published in 1988. More recently, The Cancer Genome Atlas (TCGA) has enhanced our understanding of the molecular basis of brain tumours exponentially. More precise molecular classification of brain tumours may improve the success rate of clinical trials by comparing similar molecular subtypes and lead to personalised therapeutic options for patients. The 2016 WHO classification introduces the concept of a ‘layered diagnosis’ combining histology and molecular genetics, with molecular genetics, grading, histology and final integrated diagnosis forming layers 4 to 1. This combined phenotypic and genotypic grouping puts tumours with similar prognostic markers together and guides treatment for biologically and genetically similar tumours. However, some disadvantages are unavoidable, like a delay in getting the final result due to the wait for molecular genetics testing, a potential change in the grade of the tumour with the final integrated diagnosis, and discrepancies in access to molecular analysis facilities and expertise in some parts of the world. Relevant information regarding some common paediatric tumours are presented here, but the list is not exhaustive. It aims to provide clinicians a list of the conditions usually encountered in a normal paediatric neurosurgical practice.
Diffuse midline gliomas
The new entity in this category of the classification is described as diffuse midline gliomas, WHO grade IV H3 K27M mutant. These tumours were historically termed diffuse intrinsic pontine gliomas (DIPG), occurring primarily in children in midline locations like thalamus, brainstem and spinal cord. They show K27M mutations in the Histone H3 gene H3F3A (80%), less commonly in the HIST1H3B gene (~20%) and very rarely in the HIST1H3C gene. Histones are responsible for the nucleosome structure of chromosomal fibres and play a central role in transcription regulation, DNA repair and replication, and chromosomal stability. The mutant H3.3 histone disrupts epigenetic post-translational modifications near genes involved in cancer. Histologically, they are diffusely infiltrative gliomas with predominantly astrocytic differentiation. Certain juvenile gliomas in the telencephalic hemispheres (but still midline) present with morphological appearances of a glioblastoma and genetic testing reveals an H3F3A mutation at G34 (H3F3A G34R/V). These tumours have an clinical prognosis lying between GBM IDHwt and GBM IDHmut.

Medulloblastomas
The classification of medulloblastomas (MB) was one of the greatest challenges during the creation of the WHO 2016 classification due to the usefulness of both its histological classification as well as the genetic classification. Hence, medulloblastomas have both genetically defined and histologically defined classifications. Since medulloblastomas are embryonal tumours, they are automatically assigned a WHO grade IV. The histologically defined classification consists of classic, desmoplastic/nodular and large cell/anaplastic MB. The genetically defined classification, which is new, consists of WNT activated, SHH activated and non WNT/non SHH MB. The WNT (wingless-related integration site) pathway regulates crucial aspects of cell fate determination, cell migration and polarity, neural patterning and organogenesis, whereas the SHH (sonic hedgehog) pathway has a role in the induction of the floor plate of the developing embryo and plays an important role in regulation of organogenesis later. The non WNT/ non SHH group consists of Groups 3 and 4, where group 4 tumours with chromosome 11 losses are low-risk tumours and group 3 and 4 tumours without chromosome 11 losses are standard-risk tumours. The WNT activated MBs are low-risk tumours, whereas the SHH activated MBs with TP53 mutations are high-risk and without TP53 mutations are standard-risk tumours. The non WNT/ non SHH group is the most common form of MB, accounting for nearly 60% of all MBs. In case of difficulty establishing a histological or genetic diagnosis, medulloblastomas can be termed NOS. Since expression profiling or histological analyses for molecular classification of MBs are not easily available in all institutions, the WHO have recommended a set of three antibodies to help classify these tumours. They are represented in Figure 19 above.

Other Embryonal tumours
This category includes entities like atypical teratoid/rhabdoid tumours (AT/RT), CNS embryonal tumours with rhabdoid features, embryonal tumours with multi-layered rosettes (C19MC – altered and NOS), and CNS embryonal tumours (consisting of former CNS PNET entities – medulloepitheliomas, CNS neuroblastomas, ganglioneuroblastomas and a new entity, CNS embryonal tumours NOS), all of which are given a WHO grade IV due to their embryonal origin. AT/RTs are characterised by loss of expression of either INI1 (involving mutation/loss of locus of SMARCBL1 gene) or BRG1 (encoded by SMARC4 gene). Tumours which are histologically akin to AT/RTs but express INI1 and BRG1 are termed CNS embryonal tumours with rhabdoid features. A new entity introduced in this category in the 2016 classification is ‘Embryonal tumour with multi-layered rosettes’ (ETMR), and, based on amplification of C19MC expression, they are termed ETMR, C19MC altered or ETMR, NOS (if no alteration of C19MC or if the test cannot be performed).

Ependymomas
This category has been changed little in the new classification due to the continuing (albeit diminishing) value of the existing histological classification and grading system. Histologically, WHO Grades 1 to 3 ependymomas are described:

- WHO grade I tumours – myxopapillary ependymoma and subependymoma.
- WHO grade II tumours – Epimedymoma, papillary ependymoma, tanycticependymoma, and clear cell ependymoma, and
- WHO grade III tumours – Anaplastic ependymoma.

There has been in recent research, a molecular classification of paediatric posterior fossa ependymomas which divides them into Group A,
with poorer outcomes and Group B with better outcomes. The new genetics based entity in the 2016 classification is the supratentorial ependymoma with a RELA fusion (majority of paediatric and small minority of adult tumours in this location) which is graded into WHO grade II and anaplastic WHO grade III tumours based on the same criteria as the non RELA fused ependymomas. These tumours can be tested using the antibody L1CAM which only binds to RELA-fused ependymomas. An entity called cellular ependymoma has been eliminated from the new classification due to its resemblance to a standard WHO grade II ependymoma.

Neuronal and mixed neuronal – glial tumours
This category comprises of some WHO grades I – III tumours which have not been changed very much from the previous classification system. They include dysembryoplastic neuroepithelial tumours, gangliogliomas, gangliocytes, dysplastic cerebellar gangliocytomas, desmoplastic infantile gangliogliomas, desmoplastic infantile astrocytomas and central neurocytomas (WHO grade II). To this has been added one new entity called diffuse leptomeningeal glioneuronal tumour, WHO grade I (DLGNT). These were previously termed diffuse oligodendrogial leptomeningeal tumours, and can show frequent BRAF: KIAA 1549 duplications and deletions, 1p (frequent), and, not that frequently, 19q deletions and no IDH mutations. Though they are predominantly Grade I tumours, there have been reports of malignant tumours as well. The other change in this category is that neurocytomas are now considered to be characterised by the absence of IDH mutations.

Conclusion
The 2016 molecular WHO classification reflects a quantum leap in the application of genetics to the description of brain tumours. However, the 2016 WHO classification has also highlighted the amount of work that is still necessary to achieve better genetically based classifications for many tumours such as meningiomas and ependymomas. Initiatives such as the 100,000 genomes project will further our understanding in this regard. It is vital that neurosurgeons stay abreast of these developments and work in a multidisciplinary team including neuropathologists, oncosurgeons and neuroradiologists to conduct an informed, up to date practice.
List of abbreviations:
IDH: Isocitrate Dehydrogenase
TP53: Tumour protein (gene) 53
BRAF: proto-oncogene B Raf-v-Raf murine sarcoma viral oncogene homolog B
H3 K27M: Lysine 27 to methionine substitution in histone variant H3.3
HIST1H3B, HIST1H3C: Histone cluster 1 H3 Family member B and C
WNT: Wingless-related integration site
SHH: Sonic hedgehog signalling pathway
INII: Integrate Integrase I
SMARCB1: SWI/SNF related, matrix associated, actin dependent regulator of Chromatin, subfamily B, member 1
SMARCAC4: SWI/SNF related, matrix associated, actin dependent regulator of Chromatin, subfamily C, member 4
C19MC: Chromosome 19 microRNA cluster
REL:A- Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A
LiCAM: L1 cell adhesion molecule

S several years after diagnosis, I took up Argentine tango again – it had been one of the casualties of the early years of Parkinson’s – and with two teachers began to explore the impact of the dance on my experience of the condition. We knew that exercise was good for the brain, effective in creating plasticity1 and protecting against disease,2 and that some studies suggested that dance was particularly helpful. We looked at research which compared tango with other dances3 and began to evolve a framework for presenting our findings. Essentially this would be a personal account, an insider’s view.

Inclusion was a crucial social benefit: the opportunity to dance as part of a mainstream community, to be defined as a dancer, rather than as a member of a ‘special’ class where I was defined by the disease. The challenge of holding my own in a mixed group was amplified by the physical demands of the dance. In addition to good posture and balance, tango requires conﬁdent stepping and turning, and changes in speed and direction, which may target speciﬁc movement difﬁculties associated with Parkinson’s. It is also a multi-tasking activity. We observed that responding to these multiple challenges was part of what worked, enabling me to achieve ‘beyond the restrictions caused by PD’. In the private lessons, we noted improvements in posture and ﬂuency of stepping and less upper body rigidity. In the milonga4 I felt my twitches and tremors slip away as I joined others on the dance floor. A curious effect concerned energy: fatigue had been an issue for me more or less since diagnosis. Now I found that the more I danced, the less tired I became.5

A further challenge stems from the fact that tango doesn’t have a set sequence of steps but instead is improvised, relying on unspoken sensory cue and physical support, the close embrace is often described as a ‘natural, loving hug’. The relationship between partners demand’s presence completion, a tuning in to his frequency and the core of that elusive ‘connection’ which is the goal of every dancer. Both sensory cue and physical support, the close embrace is often described as a ‘natural, loving hug’ and can be a powerful counter to the feelings of isolation which come with Parkinson’s.

And then there’s the music. The function of music as an auditory cue is well-documented.6 My experience, though, was more in line with the findings of isolation which come with Parkinson’s. My experience, though, was more in line with the profound impact of Argentine tango on my quality of life and I hope will be a useful complement to research on the more readily measurable physical beneﬁts of dance. It offers an example of living well with illness, suggesting recommendations that dance should become more widely available as part of traditional treatments.7 Perhaps it also paves the way for the patient’s voice to be heard more clearly.8 However, publication depends on the funding target, currently running at 84%, being reached. ACNR readers can help this happen by spreading the word. Find out more at https://unbound.com/books/tango/
How to reduce AF related strokes

Abstract
Atrial Fibrillation (AF) has long been known to be a strong risk factor for stroke. The prevalence of AF is increasing due to improved ability to treat chronic cardiac conditions, and the ageing population. There are three types of AF: permanent, paroxysmal and persistent. The most common criteria for diagnosis has been AF detected over 30 seconds, though there are other options. Continuous cardiac monitoring provides a better diagnostic yield than 24-hour Holter monitors. The REVEAL-AF study regarded AF detected over 30 seconds as diagnostic, and the majority of stroke physicians would not accept less than 30 seconds as diagnostic. Meta-analysis suggests outpatient monitoring for up to seven days only detects 13.6% AF compared to 23.3% with implantable loop recorder devices. Small studies have shown potential for smart phone based cardiac monitoring for ease of use compared to implantable loop recorders. Several current cardiac monitors are available to purchase e.g. Zeo device, but they are not all NICE approved.

The CHA2DS2VASC score is the most used predictor of thromboembolic events in patients with AF. NICE guidelines recommend anticoagulation for patients with a score of two or above, whilst taking their bleeding risk into account using the HAS-BLED. The European guidelines advise anticoagulation should be started with a score of one or above in men. This would remove the unexplained increased risk of stroke in women (gender scoring one in the CHA2DS2VASC), identified in several studies, when considering risk of stroke. Management of atrial fibrillation is divided into medical and interventional.

Medical Management

Warfarin
Warfarin reduces the risk of AF related strokes, without the need for bridging heparin therapy. This is primarily based on the BRIDGE study, which showed that heparin bridging in patients who needed to stop warfarin for up to five days pre-operatively did not reduce the risk of thromboembolic events (0.3% vs 0.4%), but increased the risk of bleeding (3.2% vs 1.3%).

DOACs
In 2011, three trials were published showing DOACs were neither inferior nor potentially better than warfarin for patients with AF. They were either oral factor Xa inhibitors (dabigatran (RELY)) or direct thrombin inhibitors (apixaban (Aristotle)) or rivaroxaban (ROCKET-AF), edoxaban (ENGAGE TIMI48). All of these studies showed fewer ischaemic strokes and fewer haemorrhagic events on a DOAC compared to warfarin. They are rapid acting anticoagulants with an average half-life ranging between 7-15 hours. They are all renally excreted to some degree. They are all impacted by the P-glycoprotein transporter system, and therefore drug interactions must be considered (e.g. carbamazepine, phenytoin and ketoconazole).

Warfarin has now become the second line anticoagulant of choice for newly diagnosed AF since the 2011 Direct Oral Anticoagulants (DOAC) trials were published. The main reason for this is the reduced rates of haemorrhage on a DOAC compared to warfarin, as well as better therapeutic target achievement. The NICE guidelines recommend either a DOAC or warfarin for secondary prevention, and more often than not, a DOAC is the preferred choice. Despite guidelines, many patients are underdosed on a DOAC and therefore are not benefiting from adequate treatment.

Warfarin is reasonable or necessary in patients who are already established on warfarin with no complications, patients with valvular heart...
Anticoagulants
Heparin
LMWH
Fondaparinux
Oral Factor Xa inhibitors
Dabigatran
Heparin
LMWH
Direct thrombin inhibitors
Rivaroxaban
Apixaban
Eldoxaban
Fibrin
Thrombin
VII and Tissue Factor
Va
Xa
IXa
VIII

Figure 1: Mechanism of action of various DOACs.

BOX 2: Complications of LAA closure\(^a\)
Access complications (0.6-13% requires surgical intervention)
Site haematoma
AV fistula
Retropitoneal bleeding
Device Implantation Complications
Pericardial effusion (more serious in less experienced centres)
Device migration
Dislodgement or embolisation
Cardiac perforation
Damage to adjacent structures
Post-procedure complications
Increased thrombotic risk

Surgical Management

Left Atrial Appendage (LAA) Closure
Patients with a high risk of stroke, but who cannot be anticoagulated, may be considered for LAA closure. This is theoretically feasible as the majority of the clot in AF comes from the LAA, presumably due to increased inflammation and fibrin deposition.\(^{22}\) Transoesophageal studies have consistently shown a strong association between spontaneous contrast, thrombus of the LAA and aortic plaque as high risk in AF patients.

LAA closure can be achieved using percutaneous devices such as the Watchman device. PROTECT\(^\text{TM}\) and PREVAIL\(^\text{TM}\) were randomised trials showing non-inferiority of the Watchman device to warfarin. Other less well studied devices include the LARIAT system, Amplatzer cardiac plug and WaveCrest Device. Due to the low rate but severe complications associated with the procedure (Box 2), NICE guidelines have recommended LAA closure in those deemed unsuitable for anticoagulation and only with the decision of an MDT with a clinician who is experienced with the devices.

Patient conundrums
1. When to start anticoagulation?
   It is not clear when anticoagulation should be commenced after a stroke. It is recommended to start anticoagulation two weeks after a moderate to large stroke, to prevent haemorrhagic transformation. NICE guidelines advise commencement of anticoagulation immediately after a TIA, and within a week for minor strokes.\(^{26}\) Many clinicians tend to use the 1,3,6,12 rule whereby TIAs are anticoagulated on day one, minor strokes by three days, moderate strokes by six and larger strokes after 12 days. This has no basis in literature. Two trials (ELAN and OPTIMAS) studying this particular question will be recruiting from 2018.

2. How to choose between the DOACs?
   Although the evidence does not compare the DOACs against each other, there are some factors which can aid in choosing the correct DOAC for individuals. Meta-analysis data suggests apixaban has less bleeding risk and is more cost-effective, and dabigatran has a lower bleeding risk than rivaroxaban.\(^{27,28}\)

Dabigatran and apixaban are dosed twice daily while eldoxaban and dabigatran are dosed once a day. Therefore compliance is the main factor to influence the choice of a DOAC. Rivaroxaban is metabolised via the hepatic system and therefore should be avoided in patients with liver derangement. It should be taken with food to improve its bioavailability. Dabigatran cannot be broken, chewed or opened as this reduces the bioavailability of the drug. It should be avoided in patients with a gastric bypass, peptic ulcer disease and gastrectomy. In the RE-LY study, there was an unexplained increase in myocardial infarct in the dabigatran arm, although subsequent registry data have not replicated this.

3. Should we change to DOAC if patient is already on warfarin? And when?
   There is no official guidance on this. If a patient is stable on warfarin without any complications, they should remain on warfarin. If a patient has had a stroke on warfarin, and they are within the therapeutic range less than 60% of the time, they should be switched to a DOAC. GP guidelines suggest once the INR falls below two, a DOAC can be initiated immediately.

4. When should we consider switching DOACs?
   There are no head to head trials comparing DOACs to each other. The above considerations regarding compliance and renal failure apply. If a patient develops renal failure, then it would be safer to adjust the dose of the DOAC if possible, or switch to warfarin.

5. Should we still anti-coagulate patients who bleed on anti-coagulation?
   The risk of a stroke in patients with AF remains high. Studies indicate that patients who have a haemorrhage on anti-coagulation have a higher mortality rate than spontaneous haemorrhages. There are no randomised controlled trials clarifying the safest action for patients with clear anti-coagulation needs and a recent haemorrhage. Danish registry data suggests that oral anticoagulant treatment was associated with a significant reduction in mortality, and stroke.\(^{29}\)

   This question will hopefully be addressed in the current SOSTART study, recruiting all patients with AF and an intracranial haemorrhage.

6. What to do if a DOAC fails?
   It is important at this point to ensure the pathophysiology of the stroke is understood, as well as patient compliance. Patients with a lacunar stroke will not necessarily stop having lacunar strokes on anticoagulation as the stroke is unlikely to be due to a cardio-embolic source. The same applies for patients

disease, patients with severe chronic kidney disease (eGFR <30 mL/min) and patients in whom a DOAC is contraindicated. Patients established on warfarin without any complications should not routinely be switched to a DOAC.

Reversal Agents
DOAC reversal agents are being investigated. Idarucizumab can reverse dabigatran, and has been approved in emergencies.\(^{19}\) Use of Idarucizumab did not increase thrombotic events, and most patients were restarted on anticoagulation by 90 days. Phase III randomised controlled trials have shown Andexanet alfa\(^{20}\) and aripazine\(^{21}\) are effective in reversing factor Xa and thrombin respectively. Eighteen percent of patients who received Andexanet alfa suffered a thrombotic event, although since this was an open label single group study, there is no comparison with a control arm.

Reversal Agents

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   There is no official guidance on this. If a patient is stable on warfarin without any complications, they should remain on warfarin. If a patient has had a stroke on warfarin, and they are within the therapeutic range less than 60% of the time, they should be switched to a DOAC. GP guidelines suggest once the INR falls below two, a DOAC can be initiated immediately.

4. When should we consider switching DOACs?
   There are no head to head trials comparing DOACs to each other. The above considerations regarding compliance and renal failure apply. If a patient develops renal failure, then it would be safer to adjust the dose of the DOAC if possible, or switch to warfarin.

5. Should we still anti-coagulate patients who bleed on anti-coagulation?
   The risk of a stroke in patients with AF remains high. Studies indicate that patients who have a haemorrhage on anti-coagulation have a higher mortality rate than spontaneous haemorrhages. There are no randomised controlled trials clarifying the safest action for patients with clear anti-coagulation needs and a recent haemorrhage. Danish registry data suggests that oral anticoagulant treatment was associated with a significant reduction in mortality, and stroke.\(^{29}\)

   This question will hopefully be addressed in the current SOSTART study, recruiting all patients with AF and an intracranial haemorrhage.

6. What to do if a DOAC fails?
   It is important at this point to ensure the pathophysiology of the stroke is understood, as well as patient compliance. Patients with a lacunar stroke will not necessarily stop having lacunar strokes on anticoagulation as the stroke is unlikely to be due to a cardio-embolic source. The same applies for patients
with severe carotid disease. Therefore it is not appropriate to switch DOAC treatment in patients with dual risk factors for stroke. The decision would be made based on the relative certainty that the recurrent stroke is cardio-embolic.

While there is no head to head comparison, ENGAGE did have the lowest number of stroke or systemic embolism events reported [RELY, 87/3006 (2.8%)] patients, ARISTOTLE 212/9120 (1.2%), ROCKET-AF 118/6058 (1.7%), ENGAGE 182/7035 (1.18%). It is not recommended to use this data as a reason to choose one DOAC over another, as each trial design was slightly different.

Cryptogenic Stroke

Up to 25% of strokes are cryptogenic. It is likely that the majority of these are cardio-embolic. Embolic stroke of undetermined source (ESUS) is defined for non-cardiac infarcts where the usual causes have been discounted. Navigate ESUS was stopped early due to non-superiority and increased bleeding risk between rivaroxaban and aspirin. Similar trials are underway for dabigatran (RE-SPECT ESUS) and apixaban (ATTICUS).

Conclusions

AF is very common, and a strong risk factor for ischaemic strokes. Anticoagulation is the mainstay of treatment. It is likely that the majority of these are cardio-embolic. Embolic stroke of undetermined source (ESUS) is defined for non-cardiac infarcts where the usual causes have been discounted. Navigate ESUS was stopped early due to non-superiority and increased bleeding risk between rivaroxaban and aspirin. Similar trials are underway for dabigatran (RE-SPECT ESUS) and apixaban (ATTICUS).

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New Medical Cannabis Clinicians’ Society and free online training programme

The properties and effects of medical cannabis are understandably little known about in the UK. It was never taught at University and as an illegal drug there has been no reason for our profession to learn about its medicinal properties. As a result, the overwhelming majority of doctors would, quite rightly, not prescribe it and indeed should not prescribe it without some understanding of its properties, side effects, dosage and its interactions.

Recent high-profile campaigns, especially that of EndOurPain.org have led the government to announce the re-scheduling of cannabis which opens the door to it becoming available on prescription. That’s why I am taking a lead role in the formation of a new Society which will be a forum for the exchange of knowledge and best practice in this field. I urge those doctors and other medical professionals with an interest in this fascinating subject to come together, to learn from each other, and develop a wider understanding of medical cannabis.

We are holding the first seminar of the new Medical Cannabis Clinicians’ Society, as well as launching a free on-line training programme on Monday 5th November 2018 at the RAF Club, 128 Piccadilly, London, W1J 7PY. I very much hope that readers and their colleagues will feel able to attend. Contact for enquiries is info@UKMCCS.org and tickets for the event are available via www.ukmccs.org

Professor Mike Barnes
Exome sequencing reveals an unusual cause of carpal tunnel syndrome

Abstract
Carpal tunnel syndrome (CTS) is a common diagnosis in the neurophysiology clinic. A clinician usually considers occupational, anatomical or systemic causes for CTS. Mucopolysaccharidoses may not be considered in patients presenting in adulthood. In this context we present the case of a male patient referred to the service with CTS aged 20. Genetic investigation was initiated due to additional features including epilepsy, arachnoid cysts and cardiac valvular anomalies, as well as a family history positive for CTS. Exome sequencing identified homozygous p.Glu276Lys mutations in IDUA, confirming a diagnosis of attenuated mucopolysaccharidosis type 1 (MPS1). This case demonstrates the wide clinical spectrum of MPS1, and highlights clinical pointers to aid its recognition.

Introduction
Pain or paraesthesia in a median nerve distribution is common in adults and typically leads to a diagnosis of carpal tunnel syndrome (CTS), which may be confirmed by neurophysiological testing. Although CTS can occur in isolation, due consideration should be given to the exclusion of underlying precipitants, such as diabetes mellitus, hypothyroidism or inflammatory arthropathy. Lysoosomal storage disorders, such as mucopolysaccharidoses, represent an important differential diagnosis in the rare instances of CTS presenting in childhood. This differential is much less likely to be considered in adults, when additional features such as intellectual disability or dysmorphic facial features are absent. In this context, we present a case report of an adult male presenting with bilateral CTS, in whom exome sequencing identified biallelic mutations in IDUA, consistent with a diagnosis of attenuated mucopolysaccharidosis type 1 (MPS1).

Case Report
A 20-year-old male (patient 1), an allied health professional, was referred to adult neurology services, complaining of intermittent sensory symptoms in his hands, and complete hypoesthesia in the index and middle finger of his left hand. On closer questioning, the patient recalled tiptoe-walking as a child, intermittent sensory symptoms in his hands and feet, “clawing” of fingers, and weak grip from his early teenage years. There was a history of aortic and mitral regurgitation and ventricular septal defect repair aged 11. He previously attended paediatric neurology services aged 13 and had left sided carpal tunnel release aged 17.

On examination, thenar wasting, particularly on the left, and in both extensor digitorum brevis muscles was noted. He had high arches, flexion contractures of toes, and tight Achilles tendons. There was distal muscle weakness, particularly in the upper limbs, and brisk lower limb reflexes. Plantar responses were flexor. Spinal rigidity was also noted. He had no coarse or dysmorphic craniofacial features. Shortly after this presentation, aged 21, the patient developed generalised seizures, and was diagnosed with epilepsy.

MRI of brain showed prominence of CSF spaces, including those surrounding brainstem. Moderately-sized bilateral arachnoid cysts were seen in anterior aspects of middle cranial fossae with dysplastic temporal lobes. (Figure 1).

Figure 1: Axial T2-weighted MRI of brain at age 21 (patient 1) demonstrating prominence of CSF spaces for age and bilateral arachnoid cysts anterior to the temporal lobes.
Family history revealed that his parents were first cousins. Two siblings were diagnosed clinically with ‘Charcot Marie Tooth type V’ in childhood, and had previous surgery for CTS. Both had completed university level education, and displayed similar clinical features including high arched feet with hammer toes (Figure 2), and thenar muscle wasting. Investigations revealed cardiac abnormalities, arachnoid cysts and mild corneal clouding in one of the siblings.

Clinical details of the proband (patient 1) and affected siblings (patient 2 and 3) are summarised in Table 1.

In Patient 2, MRI of brain demonstrated slightly more pronounced prominence of CSF spaces, and moderate bilateral middle cranial fossa cysts (Figure 3). MRI of cervical spine showed mild to moderate stenosis in mid-cervical spine and early flattening of the cord (Figure 4). Investigations of pain and crepitus of left temporo-mandibular joint (TMJ) revealed maxillofacial involvement (Figure 5).

**Table 1: Clinical findings of affected family members**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset of hand symptoms</th>
<th>Bilateral CTS</th>
<th>Pes cavus</th>
<th>Spinal rigidity</th>
<th>Spinal Stenosis</th>
<th>Arachnoid cysts</th>
<th>Corneal clouding</th>
<th>Cardiac</th>
<th>Other diagnoses</th>
<th>Alpha-L-iduronidase activity (% mean normal activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13y</td>
<td>+</td>
<td>+</td>
<td>mild</td>
<td>mild, cervical spine</td>
<td>moderate</td>
<td>mild</td>
<td>VSD repair, thickened MV, moderate AVR</td>
<td>Epilepsy</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>13y</td>
<td>+</td>
<td>+</td>
<td>mild</td>
<td>mild, to moderate cervical spine</td>
<td>moderate</td>
<td>mild</td>
<td>mild LVH, AMVL thickened</td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>10y</td>
<td>+</td>
<td>+</td>
<td>mild</td>
<td>minimal</td>
<td>small</td>
<td>-</td>
<td>mild AVR and MVR, AMVL thickened</td>
<td></td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

AVR = aortic valve regurgitation, AVML = anterior mitral valve leaflet, LVH = left ventricular hypertrophy, MV = mitral valve, VSD = ventricular septal defect, y = years

**Investigations and Results**

Neurophysiology in the proband was consistent with very severe CTS. Decompression surgery resulted in a clinical and neurophysiological improvement (Figure 6). There were no other distinctive features on nerve conduction studies or electromyography (Supplementary data S1, available at www.acnr.co.uk/TBC).

A unifying genetic diagnosis was suspected in view of the multi-system features, and similarly affected siblings. Genetic testing for PMP22 copy number, MPZ, GJB1, LITAF were normal. Biochemical screen was unremarkable, with the exception of ‘marginally elevated’ excretion of glycosaminoglycans (GAG), initially felt unlikely to be of significance. The clinical genetics service approached the research team led by Prof Jan Senderek, Friedrich-Baur Institute, Munich, in view of their special interest in recessive neuropathy syndromes. Written, informed consent was obtained for investigation of DNA from the proband, two affected siblings, an unaffected sibling and parents.
Exome sequencing revealed homozygous c.826C>G (p.Glu276Lys) mutations in IDUA in all three affected siblings. The unaffected sibling and both parents were found to be heterozygous for this mutation. This mutation was previ-
ously reported in a single Thai individual with mucopolysaccharidosis type 1 (MPS1), and is predicted to be pathogenic by in silico analysis. The diagnosis of MPS1 was confirmed by alpha iduronidase activity <1% of mean normal activity in all three siblings.

**Discussion**

This case describes a diagnosis of attenuated MPS1 made by exome sequencing in a male who presented with CTS in adulthood, without intellectual disability or overt dysmorphic facial features typical of MPS1.

MPS1 is a progressive, multisystem condition caused by deficiency of the enzyme α-L-iduronidase (IDUA) within the lysosomal degradation pathway, resulting in accumulation of GAGs and glycolipids in neurons and other tissues. Historically, MPS1 was described as three distinct entities: Hurler syndrome, a severe form with early childhood onset; the milder Scheie syndrome; and an intermediate phenotype Hurler-Scheie syndrome. However, no measurable biochemical difference has been described between these forms, and the clinical spectrum is now recognised as a continuum. In modern nomenclature, ‘severe MPS1’ is analogous to Hurler syndrome, and ‘attenuated MPS1’ to all other phenotypes.

Patients with severe MPS1 usually appear well in the first few months of life, though inguinal or umbilical hernias are common. Typically by 18 months of age, the deposition of GAGs in tissues leads to coarsening of facial features, shortened long bones with wide shafts, thickened and disordered growth plates, pelvic and hip anomalies, flattened and beaked vertebral with gibbus deformity. Hearing loss, joint contractures, chronic nasal discharge and communicating hydrocephalus are also common features. Cardiac involvement causes thickening and incompetence of valve leaflets, and cardiomyopathy. Prognosis in severe MPS1 is guarded, with death from cardiac or respira-
tory causes usually occurring within the first 10 years of life.

Those with attenuated MPS1 have poten-
tial to develop all of the end-organ effects of severe MPS1, but usually follow a milder or prolonged disease course. Age at symptom onset and the pattern of organ involvement are variable. Registry data from 78 patients with an attenuated MPS phenotype demonstrate a median age of onset of symptoms of 5.4 years, with a range from birth to 33.8 years. Of note, 67% had a history of CTS (median age of onset of 13.1 years). Older age at symptom onset was associated with a longer delay to diagnosis, highlighting that lysosomal storage disorders are less likely to be considered as a differential diagnosis amongst older children or young adults.

Haematopoietic stem cell transplant (HSCT) is currently considered standard of care for children with severe MPS1. HSCT is associated with longer survival and a reduction or delay in onset of several key sequelae, although treated patients still experience a considerable disease burden. Enzyme replacement therapy, in the form of Laronidase, is also licensed in Europe for treatment of peripheral symptoms of MPS1. While there is robust evidence that treatment with Laronidase reduces urinary GAG excretion and hepatomegaly, evidence for additional clin-
cal responses is mixed and hence its role in the treatment of adults with attenuated phenotypes remains to be fully defined. With the advent of genomic medicine, it is likely that further efforts will be made towards developing targeted genetic treatments for mucopolysaccharidoses in the near future, most notably gene therapy by viral vector.

A diagnosis of MPS1 may be suspected due to abnormal excretion of urinary GAGs, and can be confirmed by demonstrating biallelic patho-
genic mutations of IDUA on genetic testing, or deficient α-L-iduronidase enzyme activity. Despite a mildly increased excretion of GAGs in our patient, the diagnosis of mucopolysaccharidosis was not initially considered. In retro-
spect, pointers included presence of temporal arachnoid cysts, valvular heart disease, spinal rigidity and pes cavus. Corneal clouding was only identified after diagnosis, but may have been readily detectable using the slit lamp or ophthalmoscope. Furthermore, a strong family history of early-onset CTS is itself unusual. While hereditary factors likely contribute to CTS susceptibility, and reports of familial clustering exist, examples of true Mendelian inheritance are rare. A notable exception was described by Lupski et al. of a family affected by autosomal recessive Charcot-Marie-Tooth type 4C, in whom heterozygous carriers of the Arg954* mutation in SH3TC2 developed isolated mononeuropathy of the median nerve. Systemic causes of autonomic neuropathy, including amyloid neuropathy, should also be considered where a strong family history of CTS is encountered.

Finally, this case demonstrates the diagnostic power of non-hypothesis-driven genetic inves-
tigations such as exome and whole genome sequencing. This is especially important for patients whose phenotype is exceptionally mild or atypical, such that targeted testing for their condition might never be considered on clinical grounds. Collaboration between specialties is therefore key to the successful diagnosis of rare disorders, both to identify patients suspected of a unifying genetic diagnosis, and to facilitate access of such patients to appropriate genomic technologies.

**Key points**

- The spectrum of severity of MPS1 is broad, and it may present in adulthood without intellectual disability
- Clinical pointers to this diagnosis include valvular heart abnormalities, arachnoid cysts, skeletal abnor-
malities, organomegaly, joint contractures, corneal clouding and hearing loss, and a family history compatible with recessive inheritance
- Treatment options are available for MPS1, hence prompt recognition is important
- Exome sequencing is a powerful tool to identify individuals with exceptionally mild or atypical forms of known genetic disorders

**Acknowledgements**

We thank the family described for sharing their medical journey, their consent and cooperation in preparing this manu-
script. Exome sequencing and identification of the pathogenic variant in IDUA was carried out by Prof Dr Jan Senderek and the clinical genetic service at Friedrich-Baur-Institut, Ludwig-
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Medical cannabis: time for change

Abstract
Cannabis has been used as a medicine for centuries but in recent history has been made illegal worldwide. Now the barriers to use are breaking down and over 40 countries have legalised the plant for medicinal use. There is surprisingly good evidence of efficacy in a number of conditions, particularly pain, spasticity, nausea and vomiting after chemotherapy, anxiety and childhood epilepsies. The side effects in medicinal compounds are relatively mild and well tolerated, although varieties high in THC can undoubtedly cause mental health issues. Overall, the risk/benefit profile is very favourable and the Government has now recognised the need to reconsider cannabis as a medicine, to the potential benefit of many tens of thousands of people in the UK.

Out-of-date rules must not come before compassion for those who need medicinal cannabis

Nick Hurd, Drugs Minister at the Home Office, in a recent edition of The Times.

This neatly sums up the current dilemma in the UK. We do indeed have out-of-date rules that still label cannabis as a Schedule 1 drug in the Misuse of Drugs Regulations which, by definition, means that it has “no medicinal value”. That is patently untrue and the Government must at last be congratulated for recognising that fact. However, the quote also outlines the other dilemma. We are now used to prescribing medicines which have a solid evidence base, but the debate about cannabis is more based on emotion and compassion than hard evidence. This article discusses what evidence there is for the efficacy of cannabis and how we can overcome the tension between evidence-based medicine on the one hand and compassionate use of a drug that undoubtedly helps many people but without a hard evidence base on the other hand.

Background
It is regrettable that the illegal status of cannabis has impeded modern research. However, this is at last changing in many international jurisdictions. It is now legal for medical purposes in 29 US states and medicinally legal, in differing ways, in Australia, Austria, Belgium, Canada, Croatia, Czech Republic, Denmark, Germany, Israel, Italy, Netherlands, Portugal and Spain and 30 other countries. There are many tens of thousands of people in the UK (some estimate up to a million) that use cannabis for medical purposes. The government has at last reacted to increasing pressure from individual families and has set up a panel to recommend individual cases who should have access to cannabis. It now seems likely that cannabis will be rescheduled in the near future.

The Cannabis Plant
The two most studied components of cannabis are THC (tetrahydrocannabinol) and CBD (cannabidiol). However, there are many other constituents from the actual plants which include over 100 other cannabinoids and many terpenes and flavonoids. THC is psychoactive and gives the recreational ‘high’ but CBD does not give a ‘high’ and indeed can counteract some of the psychoactive effects of THC. CBD is legally available as a nutritional supplement in the UK whereas THC is not legal. There are two cannabis formulations that can be prescribed: Nabiximols (Sativex – GW Pharma) which is a natural product with about a 50:50 ratio of THC to CBD. It is licensed for resistant spasticity in multiple sclerosis. Nabilone (Cesamet) is a synthetic cannabinoid which mimics THC and can be used for chemotherapy-induced nausea and vomiting.

Endocannabinoid System
It is only recently that the scientific rationale of the effects of cannabis have been elucidated. In 1990 Matsuda and colleagues described a cannabinoid receptor in man. This was eventually called the CB1 receptor and a few years later a CB2 receptor was also identified. These receptors are not only present throughout the central nervous system but in many other peripheral tissues, including the immune system, reproductive and gastrointestinal systems as well as the heart, lung and bladder. There are natural ligands to these receptors (Anandamide and 2-Arachidonoylglycerol). The whole system, including the precursors and the metabolic pathway, is known as the endocannabinoid system. This system is involved in a whole variety of metabolic, endocrine, neural and other functions. In neurological terms, for example, it is involved in brain protection, modulation of pain, regulation of motor activity, as well as having a role in neurogenesis, neuroplasticity and memory processing. The phytocannabinoids found in the natural plant are able to mimic the effects of the endocannabinoid receptor ligands although they also have interactions with other neural transmission systems.

Evidence of Efficacy
Given that the drug has been illegal in most countries for many years there is surprising evidence of efficacy. However, more studies certainly need to be undertaken, particularly with regard to the efficacy of different strains, different THC:CBD ratios, different methods of ingestion and further investigations as to whether the whole plant is actually
more efficacious for medicinal purposes than the individual cannabinoids—the so-called “entourage” effect. So, briefly, what are the most researched indications?

**Pain**

There is a surprising amount of literature on the efficacy of various cannabis formulations for chronic pain. A recent review by Whiting and colleagues, for example, found moderate quality evidence to support the use of cannabinoids. A review for the All Party Parliamentary Group on Drug Policy Reform in the UK also found good evidence for pain relief for a variety of conditions (cancer pain, musculoskeletal pain, neuropathic pain) and with a number of different products, including the natural plant, as well as Nabiximols and the synthetic cannabinoids.

**Spasticity**

There is good evidence of the use of cannabinoids in spasticity. Most of the work has obviously been done for the Nabiximols but studies with other cannabinoids do exist.

**Nausea and Vomiting in the Context of Chemotherapy**

Cannabis is a very useful antiemetic and has been the subject of a recent Cochrane systematic review of 23 randomised controlled trials that have confirmed this.

**Epilepsy**

In the last couple of years there has emerged good evidence of efficacy of a particular CBD product (Epidiolex – GW Pharma) for the management of various drug resistant childhood epilepsies, particularly Dravet and Lennox-Gastaut. There is also now emerging evidence, although still mainly anecdotal at this stage, that indicates that a small amount of THC in addition to the CBD can be additionally beneficial. This was confirmed, for example, in the recent case of Alfie Dingley who responded to full extract cannabis oils containing both CBD and THC.

**Anxiety**

There are a few double-blind placebo-controlled studies that have shown that CBD has useful anti-anxiety effects.

The above indications are those with most useful anti-anxiety effects. The most researched indications are pain, spasticity, nausea and vomiting, and anxiety.

**Side Effects**

Obviously with any medicine we need an analysis of the risk-benefit ratio. Is cannabis safe? The answer, broadly, is yes. The side effects will generally depend on the amount of THC in the product. High THC levels can cause psychotic issues, particularly in those with a history of schizophrenia / psychosis or a family history, and in my view such a history should be a contraindication to prescribing THC – although not to prescription of CBD. However, in medicinal cannabis, generally, lower THC levels are often combined with CBD which tends to counteract the effects of THC and thus the risk of psychosis in such products is minimal. In the short term THC products can have effects such as dizziness, euphoria, drowsiness, dry mouth, confusion, disorientation, somnolence, balance problems and fatigue, whereas those effects are generally not seen in CBD products. Dependence on cannabis occurs in around 5% of users (once again those using high THC products) which compares to a figure of around 15% dependence for alcohol and 32% for tobacco.

There is a theoretical risk of lung cancer from smoked cannabis but there is no definite association and in any case smoking cannabis is not the recommended form of medical administration.

Cannabis high in THC can also impair psychomotor performance and cognition in the short term (and thus impair driving) but there is conflicting evidence regarding neurocognitive effects in the long term.

**Availability**

If cannabis has such a favourable risk-benefit ratio, why is it not more widely available? It may be, at least up to the last couple of weeks, political inertia or political prejudice although it is certainly worth noting that a majority of MPs now support legalisation for medical purposes.

The main hurdle is with regard to the licensing of the natural plant product. Approval of medicines in the UK and worldwide will generally focus on a single compound. However, cannabis contains a whole variety of cannabinoids, terpenes, flavonoids and there are several thousand different strains of cannabis with varying proportions of THC, CBD and other components. There are also many different ways of ingesting the product with wide variations of bioavailability. The medicines approval system in the UK is simply not geared to recognising such a plant product.

Many countries have got round this problem simply by developing alternative licensing systems for a plant product. Many jurisdictions have successfully controlled the quality and consistency of cannabis by approving specific suppliers, monitoring the quality of the product and making it available only through licensed pharmacies with appropriate medical prescription or supervision.

At last the UK government is taking the issue seriously and has established a cannabis panel for consideration of individual cases. There is the real possibility of rescheduling of cannabis from Schedule 1 to at least Schedule 2 of the Misuse of Drugs Regulations 2001 in the near future. This would allow doctors to prescribe cannabis legally.

We need more research on the efficacy and side effects, we need to understand the most beneficial type of cannabis and the best mode of ingestion and, more particularly, the best dosage range. There is much to be done but the work will certainly be facilitated by legalisation. It is time we moved beyond “reefer madness” to a more enlightened use of a plant which has so much potential benefit for so many people in the UK.

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Rufus of Ephesus (Ad C. 80-150.)

The scant remaining writings of Rufus of Ephesus on the brain, melancholia, and many other disorders form an ancient though important part of our neurological heritage.

Although less well known than Hippocrates (c. 460-377 BC), and Galen (c. AD 130-200), Rufus of Ephesus (c. AD 80-150) was acclaimed as one of the great physicians of the ancient Greek era. He studied anatomy, pathology, psychiatry, and a wide range of illnesses, medical and surgical, illustrated here by selected quotations. Many works of the Greek physicians were lost to Western Europe after the 5th century. In the 14th and 15th centuries, however, Western Europeans in Spain started to rediscover and reprint Arab learned tracts and those of Byzantine scholars at the fall of Constantinople in 1453.

Remnants of Rufus’s teachings were preserved in the huge encyclopedia of Oreibasios of Pergamon (c. AD 320-403), physician to Emperor Julianus. In the four to five centuries between the Alexandrian school and Galen there remain few medical writings. Some survive only in Arabic: Rufus’ influence owed much to these early mediaeval Islamic scholars.

**Rufus of Ephesus**

Rufus (Figure 1) was born in Ephesus (near modern Selçuk, Turkey), where he probably practised medicine c. AD 100. Abou-Aly discusses at length the many uncertainties amongst history scholars of his dates, education and workplaces. During the Ptolemaic Egyptian empire, (c.323 to 30 BC) a major cultural movement developed at Alexandria. Clifford Allbutt reported: His fair anatomy points perhaps to Alexandria, or possibly (nearby) Smyrna, as his school. Little is known about his life. The principal Greek biographical authority is the 10th century Byzantine encyclopaedic Suda lexicon in the reign of the Emperor Trajan (98-117 CE). However, less certain sources suggest he lived earlier. This uncertainty mirrors the sparseness of biographical information.

Galen, Oreibasios, Aetius, and Paul of Aegina, the compilers of later medical encyclopaedias, often cited him extensively. After the ninth century the Arabic world revived his work, especially his studies of melancholy. Medieval Scholars were less aware of Rufus, though citations occur in the Latin translation of the Kitab al-Hāwī (the All-embracing Book) of Rhazes. Goupyl in Paris in 1554 edited his Greek treatises with a Latin translation but the more modern scholarship of Charles Daremberg and Emile Ruelle, (Paris, 1879), made available his extant writings. Brock also gave a translation from the Greek in 1929. He followed Hippocrates in maintaining the imbalance in the four humours — blood, green bile, phlegm, and black bile: treatment was aimed to restore normal balance. A wise and esteemed physician he made several anatomical and clinical discoveries. Many of his opinions were based on therapeutic responses he observed, in the fashion of the empiricists. As Nutton remarked, “What is most striking about Rufus’s writings as people today have them is that theoretical discussion and argument are almost entirely absent.”

**Texts**

Some of his works have been lost and can be appraised only from citations and comments. The Arabic sources, Ibn al-Nadim, Ibn abī Usābiya and Ḥajjī Khalīfā, provided similar lists of Rufus’s works. The first modern edition of Rufus’ works was the Daremberg Ruelle’s edition in 1879. Accounts of over 40 titles include: On Melancholy, two treatises On the Names of the Parts of the Human Body (Onomastikon) * On Diseases accompanied by hydrophobia Treatise on the icterus and bile (=) Treatise on Gout, syn. podagra (=) Treatise on the diminution of flesh The book of diet, two treatises Treatise on the Bladder and Kidneys (Figure 2) On the interrogation of the patient (=) On Satynsis and Gonorhoea* Questions medicales * Treatise on epilepsy Treatise on memory Treatise on vertigo.

*The only writings preserved in Greek, * in Arabic, ** in Latin. All others are fragments quoted by later authors.

Rufus had many medical interests. In his texts he commended the Hippocratic corpus (450-350 BC). He dissected apes, monkeys, pigs, and other animals. He described the decussation of the optic nerves and the lentil-like capsule of the lens. He regarded the nerves as originating from the brain, and distinguished between nerves of motion and of sensation. He described the oviduct of the sheep and rightly held that life was possible without the spleen. He is remembered as the first to describe bubonic plague, and for his description of the methods of arresting haemorrhage. His work On gout was translated into Latin in the sixth century, but remained unknown till modern times.
He accurately described the guinea worm, *Dracunculus medinensis* (medina worm, serpent worm, or dragon worm), often misquoted as filarial worms (*Filarioides*). With prescience he believed the cause of gout was an accumulation of poisons in the body. In one treatise, his keen powers of observation were applied to an epidemic of the plague in recording its environmental causes, symptoms, and treatment.13 Rufus often deferred to his predecessors but he did re-examine, and sometimes corrected their claims. Dissection of human corpses was banned in his time, which frustrated him since the first Ptolemies had briefly legalised dissection for Herophilus and Erasistratus.

The Brain

Questions about the location of the soul (Aristotle’s *cardiocentric* or Herophilus’s *encephaloacentric*) were recurring arguments in Roman and Greek anatomy. Although Rufus explained the brain in a fashion similar to Herophilus and Erasistratus, he perceptively recognised that the brain, spinal cord, and nerves were composed of the same substance, whilst he distinguished them as separate anatomical entities. His dissections disclosed:

The brain is located inside the skull; it is covered by meninges; one denser and more resistant, is attached to the bone [dura mater]; the other, thinner but also resistant, stretches over the brain [pia mater]. The upper surface of the brain is called cærocase [covered]. . . the extension from the base is the parencephalon [cerebellum]; the cavities of the brain have been designated hollows [ventricles]. The membrane which lines the ventricles is called the choroid membrane. Herophilus also calls it the choroid meninges. The processes springing from the brain are the sensory and motor nerves with the help of which we are able to feel and to move voluntarily and which are responsible for all activities of the body. There are also nerves which issue from the spinal marrow; one may designate indifferently all of the marrow which descends through the vertebrae either as dorsal or spinal.14 (p. 13)

And:

The marrow [spinal cord] arises from the brain and escapes through the hole of the cranium at the occiput [foramen magnum] and descends as far as the base of the spine through all vertebrae; it is not a special substance but an extension from the brain; it is called the marrow of the back. Nervous channels [nerves], which are distributed to sense, arise and emerge from the brain: for example, to the ear, to the nose, and to other sensory parts. One of these processes comes off in front from the base of the brain, is divided into two branches [optic nerves], and inclines towards each of the eyes in the part called the basin or cavity of vision, in the form of a fossa, and which is found on each side of the nose.14

In a fragment preserved by Oreibiasios he commended inducing fever to treat convulsions, epilepsy, asthma (orthopnoea), melancholia, certain skin diseases, tetanus, and women in labour with convulsions.15 (p. 547)

**Nerves**

Rufus showed that the nerves proceeded from the brain. He divided them into those of sensibility and those of motion that were named: aisthētika [sensation] and prokaiiretika [purposeful choice/motor] (De nominatione Partium hominis p. 36). However, he credited Herophilus and Erasistratus with discovery of the nerves, noting that they first distinguished motor from sensory nerves:

‘Nerve (neuron) is a simple solid body, the cause of voluntary motion, but difficult to perceive in dissection… According to Erasistratus there are two kinds of nerves, sensory and motor nerves; the beginnings of the sensory nerves, which are hollow, you find in the meninges [sc. Of the brain], and those of the motor nerves in the cerebrum (enkephalos) and in the cerebellum (parenkephalos). According to Herophilus, on the other hand, the nerve that make voluntary [motor] possible have their origin in the cerebra (enkephalos) and the spinal marrow, and some grow from bone to bone, others from muscle to muscle, and some also bind together the joints.’ (De anatomia partium hominis)7 (pp. 71-5, 184-5.)

He recorded that Herophilus was unclear in differentiating nerves from ligaments and tendons.

Although the details of the brain’s circulation were vague and remained so until Willis’s studies (*Cerebi Anatomie*, 1664), Rufus mentions the carotid (καρωτ) vessels.18 The ancients,’ he says, (De nominatione Partium hominis p. 42) ‘called the arteries of the neck καρωτides because they believed, that, when they were pressed hard, the animal became sleepy and lost its voice; but in our age it has been discovered that this accident does not proceed from pressing upon these arteries, but upon the nerves contiguous to them.’

**Medical treatises**

*On Melancholy*

In this detailed and praised work, Rufus described the consequences of an excess of bile as ‘melancholy humour’.17 Melancholy reflected black bile as a cause for bad digestion and for madness. Worse in autumn, he noted that intense intellectual activity precipitated symptoms. Typical sadness, anxiety, fear, suspicion, and the misery of depression contrasted with periods of joy with quick powerful movements; and if unrelied the patient might die. Galen praised his knowledge of the Hippocratic corpus, and thought his treatise On Melancholy,16 the best work on the subject before his own (sic).

*Traité sur le Pouls*

A treatise on the pulse was published in early Latin editions of Galen but identified as pre-Galenic and attributed to Daremberg to Rufus. The French translation, *Traité sur le Pouls* in 1845, and in 1879 was included in Daremberg’s edition of the works of Rufus.7 Rufus considered the heart to be the seat of life, and noticed that the left ventricle was smaller and thicker than the right (De nominatione Partium hominis p. 37). He recognised that the heart was the cause of the pulse, which he defined as the diastole, and systole of the heart – terms which persisted. He also noted like Herophilus the pulmonary blood vessels:

‘to the very large and thick vessel leading from the heart to the lungs; for in the lungs conditions are the opposite of what they are elsewhere; the veins are there powerful and in nature very similar to arteries, while the arteries are weak and bear a close resemblance to veins.’ (p. 162)

*For the layman*

Although most of his treatises were addressed to medical colleagues, his manual *For the Layman* considered many diseases, and gave public health advice both for preserving health and treating illness. His advice on public health was aimed especially at travellers, the elderly, and children. We can see his pragmatism when he warned of the risks of buying a slave with a suppurring ear, which might risk serious illness to the slave and financial loss to its buyer. In this work,4 (p.104-6), he accurately described diseases of the eye, the lens, its membrane and the optic chiasm. Ophthalmia was caused by smoke, dust and sun; too much sun caused ambyopia; glaucoma was due to changed colours of the crystalline liquid [vitreous] because of dryness; and clotting of liquid between the coroides and lens caused cataract.

*Quaestiones medicinales*

Rufus’s famous treatise, Medical Questions detailed how the doctor should elicit the vital history of the patient. The final section is an extension, not a criticism, of Hippocrates’s views in *Ars, Waters, and Places*. Rufus argued the importance of local cultures, illnesses and remedies he had found in the areas of his work. He wrote:

“One must put questions to the patient, for thereby certain aspects of the disease can be better understood, and the treatment rendered more effective. And I
place the interrogation of the patient himself first, since in this way you can learn how far his mind is healthy or otherwise; also his physical strength and weakness, and you can get some idea of the disease and the part affected. First we have to ask at what time the illness began; this is most valuable both for treatment and for reckoning the critical days. … The next thing to ask is whether what has now happened is one of the diseases to which the individual patient is accustomed, or is something which has never happened to him before… it is surely not possible, is it, to find out about these in any way except by asking? … For it is justly believed that everything congenital is harder to cure than what is not. … One must put questions to the patient, for thereby certain aspects of the disease can better be understood, and the treatment rendered more effective.” 7

Although the history is most important, the ancients relied mainly on physical manifestations for diagnosis perhaps foreshadowing the current neglect of the history in favour of sophisticated imaging techniques.

On the Names of the Parts of the Human Body (onomastikón)

This concise anatomy includes position, shape, and functions – a pioneering method to explain anatomy. 16 Rufus stressed the importance of accurate nomenclature to prevent misunderstanding, observing: ‘the smith, the cobbler, and the carpenter first learn the words for metal, tools and such like. Why should it be any different in more noble arts?’ 17 (p. 133) (Figure 3) In this treatise – he described as a manual for the students of medical art – he relied on demonstration in teaching; visible (outer) parts of the body that he demonstrated on a slave, and invisible (inner) parts shown on a dissected monkey. There follows a chapter describing single (inner) parts shown on a dissected monkey. That he demonstrated on a slave, and invisible parts referred to his ideas on melancholy through an Arabic intermediary, and there are quotations of Rufus in the Continens, a Latin translation of the Kitab al-Hawāī (All-embracing Book) of Rhazes (AD. c. 854-925). But Ironically, his more important works took second place to his use of the purgative hiera.

It appears that Galen frequently cited Rufus’s texts, with and without quotation. Galen was younger than Rufus, and his occasional reference to him was complimentary: ‘Rufus is an outstanding physician very familiar with [medical] art.’ 18 However, he did not reveal how much he owed to Rufus.

More recently, Manfred Ullmann 21 has uncovered new texts, some translated into Arabic that confirm Rufus’s major contributions to Medicine.

We can share Albutt’s opinion 3 that Rufus was one of the few really independent physicians after the Christian era yet of Hippocratic clinical tradition.

Figure 3: Oeuvre de Rufus.

Most medieval European scholars were not familiar with his works. The Arabic Constantine referred to his ideas on melancholy through an Arabic intermediary, and there are quotations of Rufus in the Continens, a Latin translation of the Kitab al-Hawāī (All-embracing Book) of Rhazes (AD. c. 854-925). But ironically, his more important works took second place to his use of the purgative hiera.

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His emphasis was on his own treatments, and many of his notions of causation of disease stem from inferences he draws from therapeutic responses.

REFERENCES

Neurological Literature: Render’s syndrome

In a previous piece in this Journal published some years ago (2006), two recently published books on Asperger’s syndrome and autism were reviewed. The reviewer took exception to what he perceived to be the possible pathologisation of variants of human behaviour characterised by social impairments, all absorbing narrow interests, repetitive routines, speech and language peculiarities, problems of non-verbal communication, and motor clumsiness under the rubric of “Asperger-like syndrome” or “autism” related to failure of theory of mind, the apparent ability to attribute mental states to others.

It must be mentioned here that the evidence of Hans Asperger’s involvement in the Nazi euthanasia programme, reported in 2018, was not known at the time of the publication of these books or of the review. The term Asperger syndrome is no longer used in the most recent diagnostic systems.

The reviewer suggested the possibility of conceptualising a converse disorder characterised by what he chose to term “hypermentalisising,” the presumption of knowing others’ mind states (excessive theory of mind?). Needless to say, further experience has indicated that other authors have also considered and written about this latter possibility, not least one of the 20th century’s finest writers, Ursula Le Guin (1929-2018), but reaching rather different conclusions.

In a short story/novella entitled Vaster than empires and more slow, published in 1971, a character named Osden is initially described thus:

Mr Osden is really a very rare case. In fact, he’s the first fully cured case of Render’s Syndrome — a variety of infantile autism which was thought to be incurable. … The therapy was completely successful.3

The name Render is, by Le Guin’s admission, taken from the protagonist (Charles Render) of a story by Roger Zelazny (1937-1995), initially published as He Who Shapes in 1964 and subsequently in 1966 as The Dream Master.4 (The potential of dreams has also been explored by Le Guin, as described in a previous article in this Journal.)

Osdn is “an empath”. Indeed, as a consequence of his treatment, his autistic defence has been unlearned and he has a supernormal empathic capacity, feeling the feelings of others as well as his own. Indeed Osden’s faculty of “wide range bio-empathic receptivity” is not species-specific, “he could pick up emotion or sentence from anything that felt”. This ability equips him to be the “Sensor” of an Extreme Survey expedition to explore a new, alien world.

I had envisaged the hypothetical hypermentaliser as having “highly developed social skills, ‘team workers’ who are good at motivating other people to work for them” with an “excessive interest in other people’s business”. Osden, however, fails entirely to fit this pattern. He cannot form any human relationship, the sum of his treatment having been to “turn an autism inside out”. He is surrounded by a “smog of cheap second hand emotions” and sometimes puts his head in a polythene bag (sic) in the belief that this cuts down on the empathic noise he receives from others. He is helplessly obedient to the demands of others’ emotions, reactions, and moods. His colleagues find him arrogant and venomous, a spreader of discord, and one calls him “Mr NoSkin”, a metaphor reflected in his physiognomy: “He looked flayed. His skin was unnaturally white and thin showing the channels of his blood”. Osden reports that his original autistic defence of total withdrawal from others has been replaced by re-transmission of the negative or aggressive affects others feel towards him. The mission Commander, Haito Tomiko, thinks autism may be preferable.3

Zelazny’s Render may perhaps have had some symptoms along the autistic spectrum: “after the death of Ruth [his wife] and of Miranda, their daughter, … he had begun to feel detached. Perhaps he did not want to recover certain empathy; perhaps his own world was now based upon a certain rigidity of feeling” (Ref.4, p. 23). Osden, by contrast, having been “cured”, cannot detach.

Another potential instance of knowing too much of others’ minds is reported by Douglas Adams (1952-2001) in The Restaurant at the End of the Universe (1980), the second novel in his extremely popular Hitchhiker’s Guide to the Galaxy series. The enlightened, accomplished and above all quiet Belcerebron people of Kakrafoon are punished for this behaviour by a galactic tribunal which inflicts upon them telepathy, “that most cruel of all social diseases”. The consequence is that “in order to prevent themselves broadcasting every slightest thought that crosses their minds to anyone within a five mile radius, they now have to talk very loudly and continuously” about inconsequential subjects.6

One putative attribute of hypothetical hypermentalisers was that they were “vocative and willing to express opinions, often forcefully, however little knowledge they actually have, opinions which they can alter dramatically dependent upon the needs of the situation”. If humans struggle to intuit beyond their subjectivity, then hypermentalisers may assume that everyone else is a hypermentaliser and behave, like the afflicted Belcerebron people, accordingly. Whether that is deemed pathological behaviour is for others to decide.

The fifth edition of ‘Aphasia and Related Neurogenic Language Disorders’ presents 24 chapters divided into three sections covering Foundations and Practicalities in section one, Assessment and Treatment in section two and Related Cognitive-Language Disorders in section three.

The topics are vast and the cover is comprehensive. The chapters have been written by well-known leaders in their fields. Although skewed to an American speech and language therapy (speech pathology) readership, the editors present a valuable resource for clinical and academic speech and language therapists in the UK of all levels of experience. I would specifically recommend several of the key chapters for the teaching of student speech and language therapists.

The overview of brain imaging, how it works and its relevance, is extremely useful and relevant to all clinicians and trainees. Like many other chapters, it presents an accessible and comprehensive overview of an area that could very easily have been over-complicated. Similarly, the chapter on aphasia theory, models and classification, provides an excellent reminder of the theoretical background behind language and language impairments.

Other chapters provide an interesting insight to the very different American health care system: I read the chapter on funding and remuneration of speech-language services with fascination. I was glad of the insight into the Medicare hierarchy. Similarly fascinating, the chapter on Telepractice, provides an excellent reminder of the potential for this exciting medium for enhancing access to expert interventions. We have not really considered this approach to healthcare in great detail in the UK SLT profession, but this chapter presents useful information and evidence on the economic benefits and access opportunities which could be provided.

Finally, I was pleased to see chapters on Primary Progressive Aphasia and Dementia with the former chapter being beautifully presented with really clear and accessible diagrams, tables and resources to inform assessment, understanding and management of this condition. People with PPA may be one group who could really benefit from the use of Telepractice in the UK since specialist centres are often centrally located and local services don’t always have the skills or capacity to support these patients. Additionally, the number of people with dementia and associated communication difficulties is increasing and I was pleased to see this area of practice highlighted in two dedicated chapters.

I would recommend this book to all SLTs in clinical practice at any stage of their career, also student SLTs, teaching and academic fellows. Even though the book has a transatlantic skew, it is valuable and often fascinating resource.

Zen in the Art of Helping

In neurology we diagnose, we treat and then we discharge. If only it were so simple.

Some years ago, in another specialty, I attended a seminar given by a Buddhist monk. It was a great disappointment; there was no shaved head, no orange robe and not a single chant to take away. I did however take away a pamphlet, called “the trick of being ordinary; notes for volunteers and students”. This title struck a chord because in my upbringing “a nice, ordinary sort of person” was a mark of approval that displayed a suspicion of anyone that might be considered or might consider themselves extraordinary.

Years later, established in this career, I returned first to the pamphlet and then to this very short but rather overwhelming book. At times, when self-checking on my own approach or reason to do the job, I return to the book. It is a sure-fire antidote to the boredom of the general clinic or the back-slapping of esteemed colleagues.

The author, David Brandon, started out by running away from home in Sunderland at 13 and living rough around the UK. He went from there to qualifying as a social worker, rising to a position of leadership amongst British social workers and gaining a Professorship. He worked on homelessness, and set up Britain’s first women’s shelters, achieving so much before dying young. His book is about the very core of what all health-care, social workers, teachers and ordinary citizens do. It’s about why we help, how we help, and the things that get in the way of helping. Neurologists do what they do for many reasons, whether that be the thrill of diagnosis, the satisfaction of effective care, the pushing forwards of therapeutics, the prestigious awards or the money but I believe, and certainly hope, that most started out with the simple desire to help people.

The book, in brief, gives a brief introduction to Zen and Brandon’s own exploration of humanity, and considers compassion, how we can help and hinder our patients (for him clients), how we empower and disempower them, and how we might work with our own ego and professional narcissism. It is consoling in places yet in others deeply critical, and sometimes quite disturbing. Things that one can take for granted disempower them, and how we might work with our own ego but it does, at-least, come with self-awareness.

As neurology moves away from diagnosis and magical cure to long term multidisciplinary care, from hard neurological disease to functional illness, from targeted therapeutics to the social needs of our neurological clientele, from drugs to mindfulness for patients, from anatomy lessons to reflection for its practitioners, there might be something for many of us here. Some colleagues will consider this book too far a walk on the wild side but, should you be open-minded and interested, it is available from all good second-hand book sellers, priced around £2.50.
Epilepsy remains a significant cause of chronic morbidity and disability across the world. However, approaches to its etiologies, pathogenesis, diagnosis and management have witnessed revolutionary changes in most parts of the developed world.

It has become clear that epilepsy is not a condition with impact on the neurological system only: the vast majority of patients with epilepsy suffer from other psychiatric or somatic co-morbidities. While the psychiatric disorders associated with epilepsy have gained notable focus, the physical-somatic co-morbidities have not.

Dr Marco Mula and Dr Mahinda Yoganrajah aimed to address this issue with The Co-Morbidities of Epilepsy, an interesting one-day course, to highlight the profound impact of these co-morbidities and the vital role of multi-disciplinary approaches in managing epilepsy patients. The programme consisted of 3 sessions covering different topics from physical co-morbidities, bone health, depression and cognition, to autism, sexual dysfunction, sleep and dissociative seizures.

Epilepsy patients are five times more likely to be hospitalised for non-epilepsy related conditions compared to the general population, with up to 90% because of psychiatric conditions, and up to 50% suffering from somatic conditions such as ischaemic heart disease, diabetes, hypertension, congestive heart failure, stroke, arthritis, bone mineral deficiency and dementia and so forth. Some of these co-morbidities can be attributed to the epilepsy or to the side effects of the anti-epileptic drugs (AED). But many are independent of the epileptic activities and tend to persist even in long-term seizure-free patients. Based on the link to epilepsy it is possible to classify the co-morbidities into different categories: random, causal, shared mechanism, resultant, etc.

These co-morbidities pose real challenges, so it is not surprising to see the 21st century ultra-specialist epileptologists eager to share the management of epilepsy with specialists from other disciplines.

The course encourages neurologists (and other specialists) to take a holistic approach to management. It also raises interesting themes regarding epilepsy as a symptomatic syndrome, where it can be a manifestation of underlying pathological process(s).

It would be helpful to see more in depth inputs on the somatic morbidities associated with epilepsy (from neurological and non-neurological points of view), to run a session or presentation on illustrative imaging and video cases and to have a more interactive discussion with the audience. There is a need for better co-ordination (maybe through epilepsy nurse specialists) between different medical specialties when it comes to the management of patients with epilepsy. This point, which suggests an improved scheme of epilepsy services within the NHS, was not discussed during this course. However, it may merit inclusion next time.

This unique course will interest many neurology trainees (not only those who are heading to epilepsy sub-specialty), and even medical trainees from other fields. And with unbeatable competitive fees it leaves no excuse for trainees not to attend (given that study leaves were granted under the current work pressure in the NHS).

The course deserves much wider publicity within the neurology community on both sides of the Thames, and beyond.
ESNA Conference 2018


The 2018 Epilepsy Nurses Association (ESNA) conference was probably the best attended, and best evaluated, in the history of the Association. It was held at the Doubletree by Hilton in Bristol city centre. Fantastic sponsorship from our colleagues in the pharmaceutical industry kept costs down, meaning that we could even offer a disco after the Gala dinner for the night owls!

Held over a Sunday and Monday, attendance was more than good needing to expand the initial capacity of 80 to just over 100 and still having late enquiries. This may reflect the increasing membership of the Association which has gone up by almost a third in the last 18 months.

Conference was split into two broad themes. Sunday largely covered new initiatives, guidelines and opportunities, with Monday focused on clinical updates. The highlight of Sunday was undoubtedly the SUDEP and epilepsy risks presentation, from Sammy Ashby of SUDEP Action. She updated delegates on Epsmon, as well as giving an overview of the latest understanding of SUDEP and the steps that clinicians can take to minimise risk. Mary Spencer presented for Epilepsy Action, highlighting their new online course for patients, which delegates felt would be very useful for their practice. The one clinical session of the afternoon came from Dr Sallie Baxendale looking at non drug treatment options for people with epilepsy, concentrating on biofeedback. Sallie gave a wonderful, thought-provoking presentation with many delegates saying that they had identified aspects to take back to their practice.

The Gala dinner afforded ESNA the opportunity to recognise excellence in the field of epilepsy. Delegates were invited to present their work, and we were delighted to present the Malcolm Taylor award for Best Foster to Michael Fullerton, Erren Wheatland and Daryl Chapman for ‘living well with epilepsy – adopting a positive and person centred approach’. We were also privileged to recognise a lifetime of dedication to education in epilepsy. Brian Chappell has been instrumental in organising the professional diploma in epilepsy; the route that many nurses at this conference first took towards their specialist understanding of the condition. He also initiated and subsequently co-edited the Association’s journal, Epilepsy Care, from its inception in 2002 through to his retirement this year. It was an honour to present him with an engraved hip flask and lifetime honorary membership of ESNA as a thank you for the contribution that he’s made to the advancement and professionalism of epilepsy nursing in the UK.

The issue of valproate, the pregnancy protection programme and new MHRA guidance was thoroughly covered at the conference. The MHRA had a stand and representative, and nurses fully appreciated the opportunity to spend one-to-one time with a member of the team involved in valproate regulation. The keynote talk on Monday was delivered by Prof Peter Turnpenny, who covered the teratogenic effects of antiepileptic drugs, valproate spectrum disorder and the new MHRA regulations. Delegates summed up his presentation as ‘fascinating’. Prof Turnpenny completed his ‘two for the price of one’ contribution to the conference with a second presentation covering the genetics of epilepsy, majoring on cutting edge genomics. With interest growing in the use of ketogenic diet in adults as well as children, delegates were given a wonderful overview of the theory behind the diet and its practical application by Victoria Bittle. Patients increasingly ask about alternative, and in some cases radical therapy options, so an opportunity to hear from experts in biofeedback, diet & other forms of complementary treatment was a real treat. However, the use of cannabinoids is perhaps the most asked about of these treatments, and has obviously been making the news over recent weeks. Prof Ben Whalley, one of the UK’s leading experts in the field, gave a technical overview of where we are up to, clinical trial data and the theory behind cannabinoid use. The highlight of Monday was the fascinating overview of epilepsy surgery, including the latest data on the efficacy of vagal nerve stimulation, presented by Mr Mike Carter. One delegate commented that “they could have listened to him all day”; an interesting, engaging speaker who inspired his audience.

The ESNA AGM was also held during the conference. The Association has been involved in a number of national initiatives, such as guidelines for the education of professional carers around epilepsy awareness and midazolam, Step Together (an initiative with the Royal College of Psychiatry intellectual disability faculty to improve epilepsy care for those with intellectual disability), updating of the specialist nurse competencies, more collaboration with Epilepsy Action via the Epilepsy Alliance, and latterly involvement in the valproate stakeholders network. It is anticipated that ESNA will continue to contribute to updates from NICE & SIGN. Members will now have a wonderful new benefit; online access to Epilepsia with work almost finished on the Association’s new website. This will not only organise ESNA’s online content more logically, it should also enable members to pay for membership and future conferences, online. It was also discussed that membership of the Association is not purely confined to nurses and any professional with an interest in epilepsy can become a member. Finally, delegates were reminded that there are two vacancies on the executive committee and we would particularly welcome applicants from Wales, Ireland and Scotland, as all of the current executive practice in England.

The overall feedback from conference was fantastic. Only 3% of delegates felt that their needs were partly met, with the rest stating that conference fully met or exceeded their expectations. The whole faculty was praised by delegates, as were the efforts of the organising committee. We look forward to welcoming people back to our next two-day conference in 2020 and our prescribing meeting next year.
Targeting Therapy of Alzheimer’s and Related Neurodegenerative Diseases

Conference details: 1st-4th June 2018, Nassau, Bahamas. Report by: Riqiang Yan, University of Connecticut Health Center and Peter St George-Hyslop, the Tanz Centre for Research in Neurodegenerative Diseases. Conflict of Interest Statement: None declared.

The first Fusion Conference on Targeting Therapy of Alzheimer’s and Related Neurodegenerative Diseases was held in Nassau, Bahamas from 1st to 4th June, 2018. The conference attracted scientists from countries around the world such as the USA, Canada, UK, Belgium, and Japan.

In the inaugural keynote lecture, Dr. David Holtzman from Washington University first presented a historical overview of apolipoprotein ApoE, the most well studied risk gene in association with the late onset of Alzheimer’s disease, and then discussed most recent discoveries on the role of ApoE in the control of tau aggregation. Dr. Li-Huei Tsai from Massachusetts Institute of Technology presented another plenary lecture on the topic of how microglia are activated in response to the challenge of neurodegeneration at the resolution of single cell levels and how LED lights, flicking at certain wavelength, activate microglia to engulf amyloid plaques. Both lectures received considerable attention from the audience and in discussions.

Almost all speakers at the conference presented outstanding lectures and discussed large portions of results that are not yet published. The programme had many standout talks across the four days. Dr Yadong Huang from Gladstone Institute at UCSF investigated the effect of ApoE isoforms in iPSCs-derived neurons on synaptic dysfunctions and reported how to block ApoE4 toxicity through a chemical perturbation based on the difference of 3D structure of ApoE4 vs ApoE3. Dr Mathew Blurton-Jones compared functional genomic datasets between iPSC-derived microglia from human and AD mouse models and identified unique signatures at different disease stages. Dr Riqiang Yan from University of Connecticut health presented a not yet published finding that the C-terminal of CX3CL1 controls neurogenesis in the adult and increased expression of this fragment will reverse neuronal loss in a tau mouse model. Dr Richard Mayeux from Columbia University discussed mutations of certain genes that are preferentially associated with certain racial groups. Ultra-rare mutations in SCRAP and FBXL7 are found to occur more frequently in the Caribbean Hispanic population while AKAP9 is a risk factor for the Africa American population. This study is important as it reveals race-dependent risky genes that are not easily seen in conventional genetic studies using whole genome populations. Dr Philip L De Jager, another investigator from the Columbia University, presented a large network dataset constructed from over four hundred individuals’ RNA seq results and identified gene modules unique to AD and related neuropathologies. One example is that upregulation of module 5 genes is associated with increased tau protein aggregation and accumulation, which correlates with declines in cognitive function. His data analyses also captured genes from activated microglia that are clustered in AD but less obvious in multiple sclerosis. Dr Charles Glabe from UC Irvine discussed a captivating observation that amyloid plaques in one AD mouse model, 5xFAD model, evolve from intra neurons rather than the conventional thought of extra neuronal seeding theory. Chemical ablation of microglia will prevent formation of amyloid deposition. Dr Sally Ishizaka, Director of the Immuno-Dementia Division at Eisai presented the strategy for human genetic-guided drug discovery for AD patients.

Two junior fellows, Drs Cara Croft from University of Florida and Rita Cacace from University of Antwerp, also gave outstanding presentations. Cara reported the first in vitro 3D model for monitoring the progression of tau aggregation and fibrillary tangles while Rita discussed how chromosome 7q36 is associated with late onset of AD and revealed DPP6 is a candidate genes for AD, frontal temporal dementia based on their human and mouse genetic studies. Both talks generated lengthy discussions with the audience and their answers to these questions were satisfying and enlightening.

One of the most memorable components of the meeting was the active discussion after each presentation and during the refreshment breaks. There were many pressing questions and lengthy debates. One vehement argument, was even resolved through WWE-style fake fighting!

Many of the conference attendees not only contributed outstanding lectures but also recognised the need for a continuing conference in such a format. It was agreed by many that this conference has created a collegial format where attendees can have close interactions with each other and discuss the most important and updated scientific questions.

In the Alzheimer’s field, holding this conference every two years is necessary, as finding a cure for AD is so urgent – more efforts and funding resources are needed in order to enable this.

We would like to acknowledge the Conference sponsors and media partners; Eisai Ltd, Fusion Conferences, Alzheimer Disease & Associated Disorders and the Journal of Alzheimer’s Disease. Without their support it would have been impossible to have held such a wonderful conference.

Conference Chairs Dr Riqiang Yan and Dr Peter St George-Hyslop, along with Plenary speaker Dr Li-Huei Tsai, are currently deciding on a location and date for the second meeting. Once confirmed, all details will be released on the conference webpage and via Fusion Conferences’ social media. A forthcoming meeting that may be of interest is the 2nd Neurogenesis Conference, being held from March 5th-8th 2019 in Nassau, Bahamas. Oral and poster submissions are currently being accepted.
In contrast to neurosurgeons, neuro-oncology is not among the usual subspecialties that neurologists tend to embark upon. However, with the changing landscape of modern medicine, and the rising culture of the multi-disciplinary management of medical conditions, neurologists not only secure a seat, but also have a say.

Against this background, the Queen Square Multi-Disciplinary Neuro Oncology Course was launched for the first time earlier this academic year.

Organised by Dr Jeremy Rees, one of not that many Consultant Neurologists with interest in neuro-oncology, the course was run through four sessions over 9 months.

The course is an attempt to shed light on the recent developments in the field, to highlight the role different specialties can play in patient management and to present topics that can interest a wide range of medical and nursing professionals: neurosurgeons, neurologists, therapists, psychologists, psychiatrists, oncologists, etc.

The first session was on basic principles of neuro-oncology, the second was on gliomas and Teenage Young Adult Tumours (TYAT) such as medulloblastoma and germ cell tumours, the third session had neurosurgical weight as it covered benign and metastatic tumours and neoplasia-related cord compression, and the forth (and last) session was useful for neurologists as it focused on leptomeningeal metastases, neurotoxicity, paraneoplastic syndromes and primary CNS lymphoma. Ethical, legal and palliative care considerations also had their deserved place especially in the first and last sessions.

The neurologist can traditionally encounter neuro oncolodical conditions during the diagnostic stage, particularly when the patient presents with seizures, headache or neurological deficit. Notably, primary CNS lymphoma, although rare and constituting less than 2% of all primary CNS malignancies, is classically on the typical lists of differential diagnoses in neurology wards.

However, with the improving survival rate and the advances in therapeutic options patients can nowadays present with longstanding neurological complications. Needless to say, neurologists should be aware of these complications. For instance, one of the emerging topics is the adverse events associated with immuno-therapies such as blockers of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1). These novel agents play a part in the management of a wide range of malignancies, from melanomas and lung cancers to Merkel cell carcinoma and colon cancer, and their side effects can present in about 2.5% of treated patients with a myriad of neurological symptoms and signs such as aspetic meningitis, neuropathy, Guillain-Barré Strohl syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome (PRES), encephalitis and transverse myelitis.

Neuro-oncology patients also face many challenges over the course of their disease: the stress of waiting and receiving diagnosis, of coping, of having treatment, of undergoing surveillance follow up, along with the stresses of the post treatment phase, remission and possible recurrence and palliative care. These challenges are not only confined to patients with high-grade malignancies, but are also faced by patients with “benign” low-grade tumours where less support is available. Those factors should be accounted for during the neuro-rehabilitation stage within the WHO4CF framework cycle (assessment, assignment, intervention and evaluation, where SMART or MEANING goals should be established).

The course also had dedicated, and understandably popular, time for neuro-imaging and case presentations.

According to the organisers the course benefited from feedbacks collected over the four sessions, and further improvements are underway.

The course may also benefit from more interactive engagement and discussion between the presenters and the audience, from drafting a handout to accompany the lectures and from offering more subsidies on the registration fees to junior health workers and trainees.

CPD should also be sought (e.g. from the RCP), as some delegates may like to credit their attendance in their professional portfolio. This is a very informative course that is recommended for neurology trainees in all stages of their training, to gain better understanding of the multidisciplinary approaches in neuro-oncology. See page 28 for details of the next course.

**SEPTEMBER**

Royal College of Psychiatrists Faculty of Neuropsychiatry Annual Conference 2018
13-14 September, 2018, London, UK
www.rcpsych.ac.uk/training/psychiatry/ conference/training/conferences/ neuropsychiatryconference2018.aspx

SBNS & ABN Joint Autumn Meeting
19-21 September, 2018, London, UK
www.sbsonline.org.uk/index.php/conferences/london-2018

ILAE British Chapter Annual Scientific Meeting
26-28 September, 2018, Birmingham, UK
www.ilaebritishchapter.org.uk

Complex Epilepsy Study Day
28 September, 2018, Dublin, Ireland
Chair: Dr Mary O’Regan
T: 07836 650782 E. jmassocited3@me.com

**OCTOBER**

Queen Square MS Centre – Clinical Update
4-5 October, 2018, Queen Square, London, UK
E. clblundered@ucl.ac.uk

British Society of Rehabilitation (BSRM) Annual Scientific Meeting
8-10 October, 2018, Brighton, UK
T: 01992 638865, www.bsrm.org.uk

Palliative Care MasterClass, Sheffield
16-17 October, Sheffield, UK
multiplesclerosisacademy.org/events/ palliative-care-masterclass-sheffield
T: 01143 27 02 10

The Great North Neuropsychiatry Conference
18 October, 2018, Newcastle, UK
E. Helen.Lownther@nwts.nhs.uk

Sleep & Dreaming
23 October, 2018, RSM, London, UK
Book online at www.rsm.ac.uk/events/slm01

Neuroscience Ireland: Young Neuroscience Symposium
25 October, 2018, Dublin, Ireland
E. youngneurosym2018@gmail.com

Complex Epilepsy Study Day
26 October, 2018, London, UK
Chair Prof Helen Cross,
T: 07836 650782 E. jmassocited3@me.com

Advanced One Day Stroke Imaging Course
31 October, NHHN, London, UK
E. l.gill@ucl.ac.uk

**NOVEMBER**

MS Academy: MS Service Provision in the UK; the Way Forward
1-2 November 2018, Park Regis, Birmingham, UK
multiplesclerosisacademy.org/events/academy-meeting

Inaugural meeting of the British and Irish Medical Cannabis Society
5 November, 2018, London, UK
E. mille@tendocmconsulting.co.uk

Dementia Academy: Practical Dementia Diagnosis and Care
7-8 November 2018, Halifax Hall, Sheffield, UK
dementiaacademy.co/events/dementia-masterclass

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Basic Principles of Neuro-Oncology
8 November, 2018, NHHN, London, UK
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/ neurooncology

Epilepsy, Critical Care & Anaesthesia: the interface. A joint 1-day symposium
hosted by the ILAE British Chapter & The Neuroanaesthesia and Critical Care Society of Great Britain and Ireland.
departmentalacademy.co/events/epilepsy-critical-care-anaesthesia-the-interface-a-joint-1-day-symposium
E. members@ilaben.org.uk

MS Specialist MasterClass – Neurologists MasterClass
21-23 November, 2018, Halifax Hall, Sheffield, UK
multiplesclerosisacademy.org/events/ msologists-masterclass-6-module-1

West of England Seminars in Advanced Neurology (WESAN) 22-23 November, 2018, Exeter, UK
www.wesan.org.uk
Rett UK Regional Day for Families & Professionals

Conflict of interest statement: None declared.

Wales & North West at Tir Morfa, Rhyll
Thank you to Tir Morfa School, Rhyll for hosting our latest regional day in Wales. This was our first ever visit to Wales and we were blessed with glorious sunshine. It was also great to see so many new faces and meet with families that had not attend a regional event before, the feedback from them was amazing.

We had a good turn out from professionals on Friday. Everyone went away with a better understanding and greater awareness and some really good practical advice on where to get started with communication approaches for people with Rett syndrome.

We know these events are really appreciated by the families who attend and we would like to try to connect with even more families in the areas that we visit. We have tremendous support from many professional speakers who give their time to share their knowledge with families.

Our presentations from professionals talked about breathing irregularities and sleep issues, current research into why they may occur and possible future drug trials that may help to alleviate or reduce some of the issues, an update on current research into gene therapy, and legal guidance around Education, Health and Care Plans.

It was great to see that the communication and education work that Rett UK are undertaking was a popular topic, with a packed presentation room and the 1:1’s fully booked.

In addition, to professionals’ presentations, we provide the opportunity to have one to one sessions with all the guest speakers, plus a physiotherapist, music therapist and a legal professional who is able to talk families through the minefield of Education, Health & Care plans.

Our next event will be in Nottingham!
For our next Rett UK Regional Event for Families & Professionals, we will be heading to Ash Lea Special School, Oswin Road, Cotgrave, Nottingham, NG12 3PA. Our free events are open to professionals and families.

Friday 12th October
– Professional event.
1.30pm until 4.30pm
Saturday 13th October
– Families & Professional event
9.30am until 4.30pm

Please contact, Gill on 01582 798910 or email gillian.bartlett@rettuk.org for further information or to request a booking pack.

Complex Epilepsy Study Day
28 November, 2018; Taunton, UK
Chair: Dr. Andrew Mallik
T. 07816 650782, E. jmsassociated1@me.com

DECEMBER
Encephalitis Conference
3 December, 2018, London, UK
www.encephalitis.info/Event-
encephalitis-conference2018
T. 01653 695283, E. Alina@encephalitis.info

UK Stroke Forum Conference
4-6 December, 2018, Telford, UK
www.stroke.org.uk

Parkinson’s Academy: Research Engagement
6 December 2018; Halifax Hall, Sheffield, UK
www.parkinsonsacademy.co/events/research-engagement

The Essentials of Neuropsychiatry:
BNPA Neurology and Psychiatry Oxford Teaching Weekend
7-9 December, 2018; Oxford, UK
www.bnpa.org.uk

2019 – JANUARY
2nd International Conference on Microbiota-Gut-Brain Axis
17-18 January, 2019, Amsterdam, The Netherlands
www.mindmoodmicrobes.org/index.php

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Gliomas / TTYA Tumours
31 January, 2019, NHNN, London, UK
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

FEBRUARY
The Society for Research in Rehabilitation Winter Conference 2019
5 February, 2019; Nottingham, UK
www.srr.org.uk

MARCH
Parkinson’s Academy: Palliative Care MasterClass
7-8 March 2019; Halifax Hall, Sheffield, UK
parkinsonsacademy.co/courses/palliative-care

MS Foundation MasterClass
20-22 March 2019; Halifax Hall, Sheffield, UK
msmultiplesclerosisacademy.org/events/
ms-foundation-masterclass-7-module-1

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

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

Parkinson’s Academy: Parkinson’s Advanced MasterClass
18-20 June 2019; Halifax Hall, Sheffield, UK
parkinsonsacademy.co/events/parkinsons-advanced-master-class-50-module-1

29 June-2 July, 2019
www.ean.org/Copenhagen2019

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

SEPTEMBER
Parkinson’s Academy: Parkinson’s Foundation MasterClass
19 & 20 September 2019; Halifax Hall, Sheffield, UK
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 October, 2019, University of Warwick, UK
www.srr.org.uk

NOVEMBER
MS Academy: MSologists MasterClass
6-8 November 2019; Halifax Hall, Sheffield, UK
multiplesclerosisacademy.org/events/
msologists-masterclass-9-module-1

To list your event in this diary email Rachael@acnr.co.uk by 19 October, 2018.
Advanced Stroke Imaging
One Day course
31st October 2018

This one-day course for healthcare professionals provides an overview of using neuroimaging and mechanical thrombectomy to treat people who have had a stroke. This course is run by the UCL Institute of Neurology in Queen Square.

Course content
• Methods for quantifying the impact of a stroke using advanced imaging techniques – from perfusional and core infarct size to methods of imaging recovery from stroke
• Using CT and MRI scans to evaluate infarcts and haemorrhages
• The benefits and applications of mechanical thrombectomy

Lecture topics will include:
• Cerebral anatomy
• Imaging stroke recovery
• Ischaemic stroke
• Haemorrhagic stroke
• Introduction to imaging for stroke
• Endovascular treatment

Who is this course for?
Doctors in training / stroke consultants / allied health professionals working in stroke medicine. You’ll receive a certificate of attendance.

The course is accredited for CPD by the Federation of the Royal Colleges of Physicians of the United Kingdom. The fee for this course is: £200.

For more information see http://www.ucl.ac.uk/lifelearning/courses/advanced-stroke-neuroimaging
For all queries please contact: s.gill@ucl.ac.uk or ion.educationunit@ucl.ac.uk

Queen Square MS Centre
– Clinical Update
4th and 5th of October 2018
33 Queen Square, London WC1N 3BG

Most clinicians see people with MS, but many are not specialists in MS or neurology and, with increasing diagnostic dilemmas and treatment options, MS management can be daunting for the non-specialist. With this in mind, this course will cover key clinical issues in the diagnosis and treatment of MS, serving as a timely update on this rapidly advancing field. It has been designed to be accessible to clinicians who are not neurologists (but should still be of interest to neurologists) or specialists in MS. The lecturers have all been chosen for their expertise and relevant experience in practice and research.

Sessions will cover:
• Diagnosis and differential diagnosis of MS
• First line disease modifying treatments
• Disease modifying treatment escalation
• Multi-disciplinary team management
• MS nursing services
• Bladder and bowel management
• Spasticity management
• Psychosocial issues
• Pathology of MS
• Pathophysiology of MS
• Clinically and radiologically isolated syndromes
• Clinical course and prognosis in MS
• NMO, aquaporin and MOG

GPs and Consultants - £100 for one day, £150 for both
Trainees and allied healthcare workers - £50 per day, or £75 for both
CPD accreditation will be applied for.

Lunch and refreshments will be provided.
Email. d.blundred@ucl.ac.uk

FOR MORE INFORMATION AND TO BOOK A PLACE ON THE COURSE VISIT: https://www.ucl.ac.uk/ion/education/courses/other/neurooncology
Multiple Sclerosis Academy

1 & 2 November 2018 · Park Regis Birmingham

MS SERVICE PROVISION IN THE UK;
The Way Forward

Do you want to contribute to change by putting an end to MS service variation? We invite you to attend our fully funded national meeting to address the variance in MS service provision on 1st and 2nd November in Birmingham.

Access to MS services across England is very variable and this is negatively impacting the lives of people with MS. We want to stimulate ideas, generate solutions and help create change. Come and join the discussion.

Register now for your fully funded place:
https://multiplesclerosisacademy.org/academy-meeting/
Phase 3 TOLEDO study results

Britannia Pharmaceuticals Ltd has announced publication of the results of the double-blind phase of the TOLEDO study in Lancet Neurology1.

Treatment with APO-go®/MOVAPO® (apomorphine) subcutaneous infusion for 12 weeks gave significantly greater reductions in OFF time from baseline compared with placebo: −2.47 h/day versus −0.58 h/day, respectively – a treatment difference of almost 2 hours (p=0.0025) and double the change in OFF time recognised as meaningful to PD patients. These reductions were seen in the first week of treatment with APO-go®/MOVAPO® infusion.

Compared with placebo, significantly greater increases in ON time (periods with good motor control) without troublesome dyskinesia – ‘good’ ON time – from baseline were observed with APO-go®/MOVAPO® infusion: 2.77 h/day versus 0.80 h/day, respectively (p=0.0008), and patients could also reduce the dosage and number of administrations of concomitant oral PD medications significantly (p=0.0014).

APO-go®/MOVAPO® infusion is an established therapy for PD. TOLEDO is the first multicentre, randomised, double-blind trial to investigate its efficacy and safety in PD and was undertaken in 107 patients from 23 hospitals in 7 countries whose symptoms were uncontrolled despite taking multiple medications.

Clinical improvements were reflected in patients’ assessment of treatment: significantly more APO-go®/MOVAPO® infusion patients rated themselves as ‘improved’ (71%) versus placebo (18%; p<0.0001).

Professor Regina Katzenschlager, lead investigator of TOLEDO, commented: “TOLEDO is an important addition to our knowledge, providing Level 1 evidence for the first time and confirming previous observational studies. Apomorphine infusion is effective and well tolerated by patients experiencing debilitating treatment response fluctuations despite optimised treatment.”

Professor Andrew Lees, an investigator in the pivotal clinical trial that led to apomorphine being licensed for PD treatment in the UK, added: “We hope the positive results of the TOLEDO study will help ensure apomorphine infusion, which is delivered using a small, ambulatory mini-pump, is incorporated into national PD treatment guidelines.”

The TOLEDO study is sponsored by Britannia Pharmaceuticals Ltd, part of the STADA Arzneimittel AG group of companies and manufacturer of apomorphine products.


Cycling Symposium across the UK – #LetsCycleIt

The UK’s oldest surgical Royal College is switching gears and taking to the road, on the first-ever ‘Cycling Symposium’. On behalf of the 500+ year-old Royal College of Surgeons of Edinburgh, a dozen surgeons and surgeons-in-training will be setting off on 1 September on a gruelling 550-mile journey that will see them cycling part of the route with them.

On this mission, the team will conduct a series of evening masterclasses on key surgical topics. These include highlighting the importance of patients’ cardiovascular fitness prior to surgery, an update on the College’s groundbreaking anti-bullying campaign #LetsRemoveIt, as well as other subjects surrounding safety in the operating theatre. The team, led by Oxford-based Consultant Liver, Pancreatic and General Surgeon and RCSEd Deputy Surgical Director of the Regional Advisory Network, Mr Mike Silva and Academic Surgical Fellow at Oxford University Hospital and Member of the RCSEd’s Trainees’ Committee Miss Katherine Hurst, will set off from Southampton, pedalling through Oxford, Birmingham, Sheffield, Middleborough, Newcastle and Carlisle to arrive in Edinburgh after a journey of almost 550 miles. Keen cyclists are invited to take part too, by joining the surgeons and cycling part of the route with them.

The #LetsCycleIt route will be open to local cyclists, both healthcare professionals and the public. To join in any of the seven daily stages, register online beforehand via www.rcsed.ac.uk

GW Pharmaceuticals presents latest cannabidiol oral solution (CBD) data at the 13th European Congress of Epileptology

GW Pharmaceuticals plc presented a variety of data on cannabidiol oral solution (CBD) at the 13th Annual European Congress of Epileptology (ECE), which took place in Vienna, Austria from 26-30 August 2018. The studies provide additional insight into the safety and efficacy of GW’s CBD oral solution in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome, two rare and severe forms of childhood-onset epilepsy that are highly treatment-resistant. In addition, data related to the pharmacology of CBD, and its antiseizure properties, will provide additional understanding of CBD’s role in the management of such diseases. A marketing authorisation application for GW’s CBD oral solution is currently under review by the European Medicines Agency (EMA).

“GW is proud to be presenting a wealth of data on its CBD oral solution to the epilepsy community. Our comprehensive pre-clinical and clinical programmes provide an understanding of the way in which CBD exhibits anti-seizure effects and further supports its efficacy and tolerability profile in patients living with two of the most difficult-to-treat forms of epilepsy,” stated Justin Gover, GW’s Chief Executive Officer. “There is still a huge unmet medical need for effective medicines that help people suffering from severe forms of treatment resistant epilepsy, and we believe that our CBD oral solution may present an important new therapeutic option in the future.”

CBD data highlights:
Highlights include the presentation of pooled efficacy and safety data from two phase III randomised placebo-controlled trials of CBD in LGS. Phase 1 drug-drug interaction data on the co-administration of CBD and clobazam, and the potential role of GPR55 and the TRPV1 receptor-dependent interaction in the anti-epileptic properties of CBD.

The full list of GW titles presented can be found on ACNR’s website at www.acnr.co.uk/category/news-review/
Young Epilepsy and Veriton Pharma Ltd announce key partnership agreement

Young Epilepsy and Veriton Pharma Ltd (Veriton) have announced a key agreement, where the organisations will work in partnership to deliver the “Rules 4 Schools” element of the charity’s newly launched ‘InTheMoment’ initiative.

Through this initiative, Young Epilepsy is looking to improve opportunities for the 55,800 school aged children with epilepsy in the UK. Starting with the ‘Rules 4 Schools’ campaign, the key aim, supported by Veriton, is to challenge current thinking and encourage systemic change.

Since 2014, all state schools in England are legally required to have a policy on supporting children with medical conditions such as epilepsy. However, Young Epilepsy believe many schools have some way to go in providing adequate support.

Matt Robertson from Young Epilepsy stated: “Schools need to make sure that children with epilepsy have the support they need to fulfil their potential in an inclusive and safe environment. In a survey we carried out in 2017, we found that 1 in 3 (36%) young people with epilepsy still don’t have an Individual Healthcare Plan at school and only 51% of families surveyed said that school staff had been trained to support a young person with epilepsy.”

The ‘Rules 4 Schools’ campaign will concentrate on four key areas: 1. Encouraging or working with schools to ensure all young people with epilepsy have an individual healthcare plan 2. Encouraging or working with schools to have a policy on supporting pupils with medical conditions 3. Achieving a requirement on schools to publish medical conditions policies on their websites 4. Campaigning for school inspections to include a routine check for support for pupils with medical conditions

Matt Robertson commented “We are delighted to be working in partnership with Veriton on this critically important campaign and we really look forward to making a difference to as many young people with epilepsy as possible through the #InTheMoment - Rules 4 Schools initiative.”

For more information about Young Epilepsy and the campaign, please visit www.youngepilepsy.org.uk/rules4schools and www.youngepilepsy.org.uk and https://inthemoment.org.uk

Livanova hosts neuromodulation symposium at ILAE British Conference

‘Where is the potential? Measuring the effects of neuromodulation’ will take place at the ILAE British Conference in Birmingham on Wednesday 26 September 2018, 12:15 – 13:45pm.

Neurostimulation is making its way into the therapeutic armamentarium of epileptologists, with several invasive neurostimulation modalities available today. At this symposium, Prof Vonck introduces the concept of a prestimulation evaluation protocol, consisting of a series of rationally chosen investigations that evaluate the presence of biomarkers for response to various neurostimulation therapies. These biomarkers should reflect the susceptibility of the individual’s epileptic network to a given neurostimulation technique. Prof Vonck will provide a framework that may be more applicable in the near future when pre-clinical research progresses can be translated into human applications.

Dr Barbara Wysota, Neurology Consultant, University Hospital of Birmingham will discuss how mechanisms of vagus nerve stimulation (VNS) are well documented on a brainstem level. However, beyond this level mechanisms become complex affecting multiple structures and networks and consensus is therefore lacking. New quantitative EEG methods can help to understand how brainstem modulation affects cortical rhythms.

The complex epilepsy and surgery team at Queen Elizabeth Hospital Birmingham were the first to assess and publish outcomes of a large cohort (n=113) of patients receiving responsive VNS therapy for refractory epilepsy. Data was collected from patients who had a responsive VNS device implanted over a three-year period between 2014 and 2017 by speaker and neurosurgeon Mr Ramesh Chelvarajah. Results from this initial study suggest a more rapid onset of seizure frequency reduction with responsive VNS Therapy than with conventional VNS Therapy.

4. Campaigning for school inspections to include a routine check for support for pupils with medical conditions

Biogen deeply disappointed by NICE Appraisal Consultation Document

The National Institute for Health and Care Excellence (NICE) has published its Appraisal Consultation Document (ACD), outlining a ‘minded no’ for the routine funding of Spinraza® (nusinersen) for the treatment of 5q spinal muscular atrophy (SMA) – a debilitating and life-threatening muscle-wasting rare disease, which takes away a person’s ability to walk, eat and ultimately, breathe. Children with the most severe form of SMA rarely live to see their second birthday.

Terry O’Regan, Vice President and Managing Director of Biogen UK and Ireland, said: “We are very disappointed that NICE has issued a ‘minded no’, however we are not surprised given the challenges of assessing rare disease medicines via the standard technology appraisal (STA) route, and our expressed reservation of the suitability of this route for evaluating medicines such as nusinersen. Sadly, this decision and the lengthy timeframe of the whole process highlights the UK challenge in providing access to rare disease medicines in a timely manner, similar to other leading economies. To date, 20 European countries including Scotland (and more across the world) have already made nusinersen available. We share the concerns of the SMA community, and remain focused on finding a way to make this important treatment available to patients who may benefit throughout the UK as soon as possible. We urge NICE and NHS England to continue to work with us on agreeing the terms of a managed access agreement (MAA) so that patients in England, Wales and Northern Ireland can share equality in access compared to other countries across Europe and the world.”

Biogen will be responding to the specific points raised in the ACD to clarify and provide further clinical and economic evidence for nusinersen, and are fully prepared to work alongside NICE and the NHS to address budget impact, sustainability and risk-sharing to manage the access to nusinersen appropriately. However, collaboration and flexibility on how the above challenges are addressed within the STA process will be central to the achievement of a MAA. Biogen’s ambition remains focused on securing access to nusinersen for all those who could benefit from the treatment.
The primary safety endpoint was the incidence of adjudicated major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH).

*Following initial use of heparin for at least 5 days in VTE.

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients; clinically significant active bleeding.
- Hepatic disease (bilirubin ≥ 1.5 x ULN).

Precautions for use:

- Haemorrhagic risk: Use with caution in patients with increased risk of bleeding such as elderly on ASA and should be discontinued if severe haemorrhage occurs. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available.

Adverse events:

- Common: headache, dizziness, rash, pruritus, maculopapular rash, gastrointestinal disorders, upper abdominal pain, diarrhoea, constipation, nausea, vomiting, haematemesis, melena, epigastric pain, dyspepsia, flatulence, change in bowel habits, altered taste, stomatitis.
- Uncommon: hypersensitivity, intracranial haemorrhage (ICH), intracranial haemorrhage, haemorrhage at the implantation site of a pacemaker/implantable cardioverter defibrillator, subdural haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal.

*References:
2. LIXIANA® Summary of Product Characteristics.

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