ISSN 1473-9348 VOLUME 17 ISSUE 4 MAY-JULY 2018

ACNR

www.acnr.co.uk

ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

NUTRICIA
Advanced Medical Nutrition

COMPLEX EPILEPSY STUDY DAYS

13 APRIL 2018: MANCHESTER, Chaired by Dr Archana Desurkar
28 SEPT 2018: DUBLIN, Chaired by Dr Mary O'Reegan
26 OCT 2018: LONDON, Chaired by Professor Helen Cross
28 NOV 2018: TAUNTON, Chaired by Dr Andrew Mallick

• CPD accredited • Free to attend • Lunch & refreshments provided

Arranged for Paediatric Neurologists, Paediatricians and Epilepsy Nurse Specialists looking to learn more about complex epilepsy and how it can be effectively managed.

For further information or to register your place, please contact Jacqui McAleer on 07836 650782 or jmassociates1@me.com

CONTENTS

MAY-JULY 2018

REVIEW ARTICLES

ABNT

SPECIAL FEATURES

REGULARS

ACNR
Published by Whitehouse Publishing,
1 The Lynch, Mere, Wiltshire, BA12 6DQ.
Publisher. Rachael Hansford
E. rachael@acnr.co.uk

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

COURSE ADVERTISING
Rachael Hansford, E. Rachael@acnr.co.uk

EDITORIAL
Anna Phelps E. anna@acnr.co.uk

PRINTED BY Warners Midland PLC T. 01778 391000

ACNR's paper copy is published quarterly,
with Online First content and additional email updates.
Sign up at www.acnr.co.uk/
subscribe-to-acnrs-e-newsletter

@ACNRJournal /ACNRjournal/

The Tom Isaacs Award 2018

Nominations are invited for the Annual Tom Isaacs Award co-created by the Van Andel Research Institute (VARI) and The Cure Parkinson's Trust (CPT). Set up in memory of Tom Isaacs, the late co-founder and president of CPT, this award recognises a researcher who has shown the greatest impact on the lives of people living with Parkinson's and has involved people with Parkinson's in a participatory way in their work.

Diagnosed at the age of 26, Tom Isaacs was one of the best known Parkinson's advocates in the world. He believed that a cure for Parkinson's can and will be found, but greater value will be gained from working with people with Parkinson's in this quest.

More information can be found at:
https://www.cureparkinsons.org.uk/forms/ti-award-nom-2018

UKABIF Film Award 2018 now open for entries

The United Kingdom Acquired Brain Injury Forum (UKABIF) Film Award 2018, sponsored by Elysium Neurological, is now open for entries from everyone that has an interest, or experience, in Acquired Brain Injury (ABI).

This year's UKABIF 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 that are being discussed by the All Party Parliamentary Group on ABI i.e. neurorehabilitation in hospital and/or in the community, or about brain injury in the context of school, prison or sport.

Andrew Bateman, UKABIF Chair said: "We've launched the Film Award in Brain Awareness Week to raise awareness of ABI and the need for neurorehabilitation. A 30-second film will have social media applications so entries must be relevant, impactful, and very much to the point. The winners will be announced at our Annual Conference on the 5th November 2018".

Joy Chamberlain, Chief Executive Officer, Elysium Healthcare said: "We're delighted to be sponsoring this Film Award. Neurorehabilitation is an essential part of the patient care pathway following an ABI, and it will be interesting to see how entrants get that message across in their films".

UKABIF is encouraging entries from individuals with a brain injury, their families or carers, students, the general public, care providers and voluntary organisations, as well the rehabilitation multidisciplinary team, doctors in primary and secondary care, case managers, personal injury lawyers and social care workers. The UKABIF Film Award is open to UKABIF members and non-members in the UK. There are four prizes of £250 to the winners. The deadline for entries is the 28th September 2018 – films entered after this date will not be considered. Winners will be announced no later than the 5th November 2018.

For further information and details on how to enter please visit: www.ukabif.org.uk/filmaward

---

Enter The WFNR Franz Gerstenbrand Award

The World Federation for Neurorehabilitation (WFNR) is encouraging clinicians, researchers and allied health professionals in the field of neurorehabilitation to enter the 2018 WFNR Franz Gerstenbrand Award. This annual Award, in honour of the eminent neurologist Professor Franz Gerstenbrand, is worth $3000 to the winner. The Award recognises and rewards a neurorehabilitation project that has benefitted patients.

Entries for the WFNR Award can come from any aspect of neurorehabilitation, for example a patient or clinic management initiative, research project, best practice development or the use of a new technological development. The Award encourages all professionals working in the field to enter, and special consideration is given to applications from those under 30 years of age. The Award is open to WFNR members and non-members worldwide. The single prize will be awarded as either a travel bursary to a clinical conference, professional development course or research project.

The deadline for entries is 30 November 2018, for more information and an application form visit: http://wfnr.co.uk/education-and-research/wfnr-award/

Michael Zandi Co-Editor.

In this issue JMS Pearce (Hull) discusses Gerhard Hansen's contribution to the study of leprosy, in the context of the work of Pasteur and Koch in the 1860s and 1870s, a brief clash with Neisser, and fall from grace in court in Bergen.

Harsha Narayanamurthy, Peter Whitfield, and Kathreena Kurian (Bristol and Plymouth) distil the 2016 World Health Organisation classification of adult brain tumours, which takes a molecular approach to help develop personalised medicine.

Zheyu Xu and Kirstie Anderson (Newcastle) highlight the pitfalls of the commonly-prescribed Z-drugs (non-benzodiazepine receptor drugs for insomnia) with an indepth analysis of the literature.

We have our conference reviews and previews, a personal perspective by Mark Smith and Gemma Kelly, and Rhys Davies (Liverpool) reviews Javier DeFelipe's latest book on Cajal, *Cajal's Neuronal Forest: Science and Art*. We hope you enjoy this issue.

Mike Zandi, Co-Editor
Email. Rachael@acnr.co.uk

Editorial board and contributors

Michael Zandi MA, MB, BChir, PhD, MRCP is Co-Editor of ACNR, a Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Honorary Senior Lecturer at the UCL Department of Molecular Neuroscience, where he works on autoimmune encephalitis, and Consultant Neurologist at the Lister Hospital, East and North Hertfordshire NHS Trust.

Todd Hardy Dr Todd Hardy BSc (Hons 1), PhD, MBBS, FRACP, is Co-Editor of ACNR and is a Staff Specialist Neurologist at Concord Repatriation General Hospital, Clinical Senior Lecturer in Neurology at the University of Sydney, and Co-Director of the MS Clinic at the Brain and Mind Centre. His main interests are multiple sclerosis and other immune-mediated central nervous system disorders.

Ann Donnelly MB ChB BSc (Clin Neurosci) MRCP is Co-Editor of ACNR and a Neurology Registrar at the National Hospital for Neurology and Neurosurgery. She completed undergraduate training at University of Glasgow Medical School, with Neurology postgraduate training at Kings College Hospital, National Hospital for Neurology and Neurosurgery, and Guys and St Thomas'. She is interested in NeuroRehabilitation with a focus on patients with multiple sclerosis.

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

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

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

Rhys Davies MA, BMBCh, PhD, MRCP, is Editor of our Book Review Section. He was accredited as a Consultant Neurologist on the specialist register in 2009 and is currently a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Yssbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.

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

David Werring FRCP, PhD, FESO, is ACNR's Stroke Editor. He is Professor of Clinical Neurology at UCL Institute of Neurology, Queen Square, and Honorary Consultant Neurologist at University College Hospital and The National Hospital, Queen Square.

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

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

Valerie Voon, MD, PhD, is a Wellcome Trust Intermediate Fellow in Clinical Neurosciences and an Honorary Consultant Neuropsychiatrist at the University of Cambridge. She subspecialises in neuropsychiatric aspects of movement disorders. She is on the Board of Directors of the British Neuropsychiatric Association and the Chair of the Research Committee for the American Neuropsychiatric Association.

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

The 2016 WHO Classification of adult CNS tumours – the essentials

Harsha Narayanamurthy
MBBS, MRCS, is a Specialty Registrar (ST7) in Neurosurgery on the Severn and Peninsula Deanery training programme, and is interested in Neuro-oncology, tumour genetics and novel approaches to brain tumour treatment.

Peter Whitfield
BM (Distinction in Clin Med), PhD, FRCS Eng., FRCS, SN, FHEA is a Consultant and Associate Professor in Neurosurgery. He is Chairman of the SAC in Neurosurgery and the Fellowship of the European Board of Neurosurgery Examination. His clinical practice is wide, encompassing traumatic brain injury, subarachnoid haemorrhage, brain tumours, hydrocephalus and degenerative spine disease.

Kathreena Kurian
BSc (Exp Pathol), MBBS, MD, FRCPath (Neuro) is a Reader in Brain Tumour Research at the University of Bristol and Honorary Consultant Neuropathologist, North Bristol Trust. She runs the Brain Tumour Research Centre; Institute of Clinical Neurosciences, Bristol Medical school which aims to reduce the burden of brain cancer by identifying risk factors and biomarkers that will inform prevention, personalised diagnosis and treatment.

Correspondence to:
Mr H Narayanamurthy,
Department of Neurosurgery,
Southmead Hospital, North Bristol NHS Trust, Bristol.

Conflict of interest statement:
None declared.

Provenance and peer review:
Submitted and externally reviewed.

Date first submitted: 20/5/17
Date resubmitted after peer review: 29/4/18
Acceptance date: 9/5/18

To cite: Narayanamurthy H, Whitfield P, Kurian K. ACNR 2018;17(4):5-8

Abstract
Brain tumour classification provides a cornerstone for understanding tumour behaviour. The 2016 WHO classification of CNS tumours combines traditional histological grading with molecular genetics and introduces the concepts of 'layered diagnosis' and 'integrated diagnosis'. An understanding of the basic concepts and important differences from the earlier WHO classifications is essential to guide clinical decision making. This paper aims to outline the key features of the 2016 WHO classification.

Introduction

From Rudolf Virchow's classification in 1863,[1] through the seminal papers of Bailey and Cushing in 1926 explaining the relations between the developing brain and brain tumours,[2] to the concept of tumour grading introduced in 1949 by James Kernohan and colleagues[3] there have been many significant contributions in this field. Zulch et al published the first WHO 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.[4] Recently, partly as a result of The Cancer Genome Atlas (TCGA), our understanding of the molecular basis of brain tumours has grown 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 introduced the concept of a "layered diagnosis"[5] combining histology and molecular genetics. Layer 4 describes the molecular genetics, Layer 3 the grading, Layer 2 the histological features and Layer 1 being the final integrated diagnosis. 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 inherent, 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 also, discrepancies in access to molecular facilities and expertise in some regions of the world. Relevant information regarding the commonest adult tumours are presented in this article, but the list is by no means exhaustive. It aims to provide clinicians a list of the conditions regularly encountered in a busy neurosurgical department.

There have been many changes introduced by the 2016 WHO classification, including loss of certain entities and introduction of new entities and variants based on a tumour's combined histological and genetic characteristics.

Glioblastomas

Glioblastomas (GBMs) are highly malignant CNS tumours, with a reported incidence of 3.19 per 100000 person-years. With the best available

Table 1: 2016 WHO grading of selected CNS tumours.[6]

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

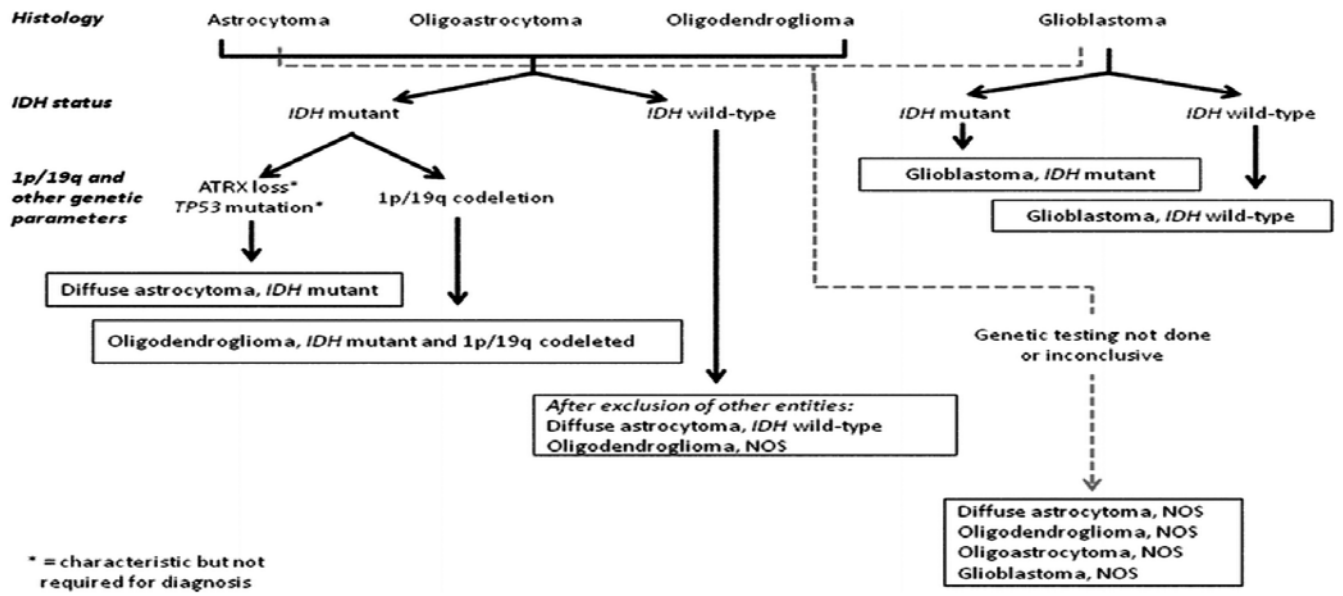


Figure 1: An algorithm for classification of diffuse gliomas based on histological appearances and molecular genetics.[6]

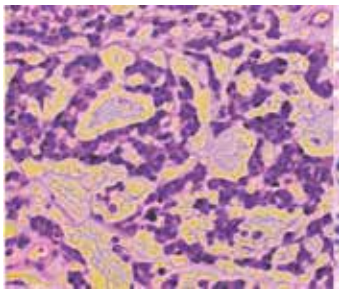


Figure 2: GBM with adenoid pattern.

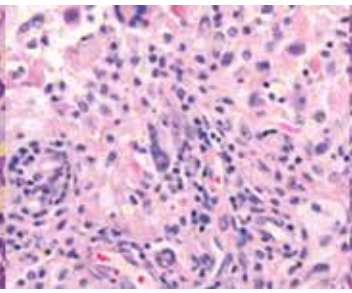


Figure 3: GBM with epithelioid/ rhabdoid pattern.

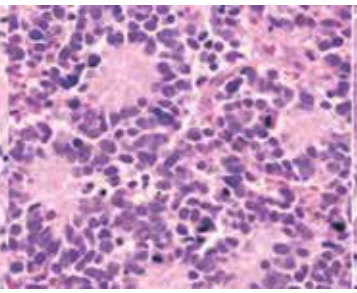


Figure 4: GBM with primitive neuronal pattern.

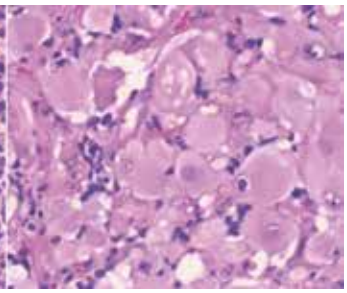


Figure 5: GBM with granular cell pattern.

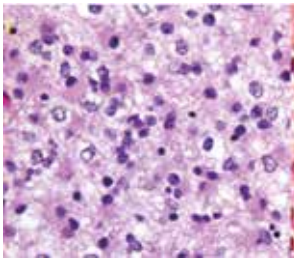


Figure 6: Diffuse astrocytoma WHO grade II.

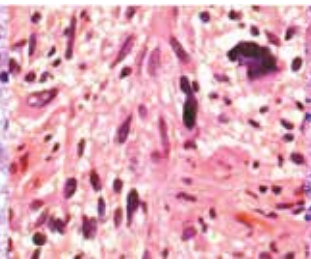


Figure 7: Anaplastic astrocytoma WHO grade III.

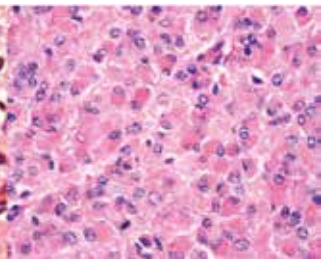


Figure 8: Gemistocytic astrocytoma WHO grade II.

treatment which includes maximal surgical resection and adjuvant radio and chemotherapy, the medial survival of patients stands at around 14 months from first diagnosis. With the understanding of the molecular basis of these tumours, many novel therapies aimed at the molecular structure of the tumours are being developed.

IDH mutation status subtypes

GBMs have now been classified based mainly on the IDH mutation status.[7] IDH wild-type (lacking the mutation) and IDH-mutant are the 2 main newly defined entities. IDH wild-type GBM corresponds to the lesions previously described as primary glioblastoma and predominate in older patients whereas IDH mutant GBM, earlier known as secondary GBM, usually arises within a lower grade glioma and preferentially arises in younger patients.[8]

While IDH status is commonly assessed immunohistochemically using the R132H IDH1 antibody, patients who are 55 years and younger and negative by immunohistochemistry should ideally be sent for IDH1/2 sequencing to identify rarer IDH1/2 mutations.

The presence of IDH mutations is strongly predictive of a better outcome in secondary GBMs.[9] Isocitrate dehydrogenases 1 and 2 (IDH1 and 2) are enzymes that convert isocitrate to α-ketoglutarate (αKG). Mutations of IDH1 and 2 bring about neomorphic activity, resulting in conversion of αKG to an oncometabolite called D-2-hydroxyglutarate (2-HG), the accumulation of which blocks cellular differentiation. This has led to the development of mutant IDH inhibitors (still in Phase 1 trials) which inhibit epigenetic dysregulation and induce cellular differentiation,[10] leading to the hope of tailored treatments for patients with specific mutations.

Other GBM variants

A new variant called epithelioid glioblastoma has been added to the IDH wild-type category, joining others like giant cell glioblastoma and gliosarcoma. Typically seen in children and young adults, it harbours a BRAFV600E mutation in about 50% of cases.[11] Another new addition to this category is GBM with primitive neuronal component (showing well demarcated nodules with primitive cells having neuronal differentiation, loss of GFAP expression, Homer-Wright rosettes, and an affinity for CSF seeding).[12] Adenoid GBM mimics adenocarcinoma (pseudoepithelial pattern). Granular cell GBM shows presence of bland-looking granular cells typical of granular cell astrocytoma, along with features like frequent mitoses, pseudopalisading necrosis and endothelial hyperplasia. Historic entities like Gliomatosis cerebri and Primitive Neuroectodermal tumour (PNET) have been removed from the 2016 WHO classification. Gliomatosis is instead used to describe a pattern of spread of glioma.[13] A category of

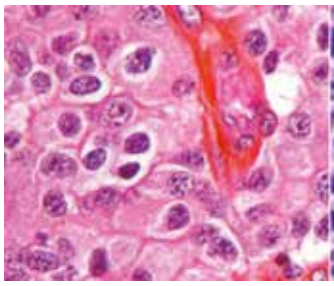


Figure 9: Oligodendroglioma WHO grade II.

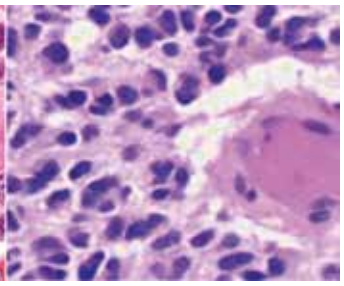


Figure 10: Anaplastic oligodendroglioma WHO grade III.

glioblastoma NOS has been created for when full molecular evaluation cannot be performed.

Astrocytomas (Diffusely infiltrating astrocytomas)

Astrocytomas originate from immortalised astrocytes and have grades I – IV based on histological properties and presence of malignant features. The incidence is 5.4 per 100000 population. GBMs are grade IV astrocytomas. With optimal treatment, the prognosis for Grade I lesions (pilocytic astrocytomas, predominantly paediatric tumours) is >10 years, Grade II >5 years, and Grade IIIs 2-5 years.[14]

Astrocytomas are now defined by the presence or absence of IDH mutations and categorised as IDH mutant or IDH wild-type astrocytomas. If an R132 IDH1 immunohistochemistry assessment is negative, IDH sequencing should be performed in all cases. If determination of IDH status is not possible, the term NOS is allowed to be used. Hence, the terms now in use are:

- Diffuse astrocytoma, WHO grade II, IDH mutant (mut), wild-type (wt) and NOS (the term diffuse astrocytoma now encompassing earlier fibrillary and protoplasmic variants)
- Gemistocytic astrocytoma WHO grade II IDH mutant; and
- Anaplastic astrocytoma WHO grade III IDH mutant, wild-type and NOS.

In nearly all cases of diffuse astrocytoma WHO grade II, IDHmut, there are TP53 mutations, and, in a majority, ATRX mutations can be found.[15] Anaplastic astrocytomas exemplify the use of the layered diagnostic pathway; IDHwt are similar to GBM IDHwt in both genetic profile and prognosis and fare worse than GBM, IDHmut.[13]

Oligodendrogliomas

Oligodendrogliomas, according to the 2016 WHO classification, are defined as diffusely infiltrative gliomas with both IDH mutation and 1p/19q co-deletion. These can now include tumours that resemble astrocytomas phenotypically, but have the necessary genetic markers of IDH mutation and 1p/19q co-deletion.[7] The presence of the 1p19q co-deletion improves overall survival in patients treated with radiotherapy and adjuvant chemotherapy comprising procarbazine, lomustine and vincristine.[16] The incidence of oligodendrogliomas is calculated to be around 5-19% of all intracranial tumours and 25% of all gliomas. Median survival for Grade IIs is around 4-10 years and 3-4 years in Grade III lesions. Oligodendroglial tumours, NOS is a category used when it has not been possible to carry out molecular evaluation. The vast majority of oligodendrogliomas (along with IDH wild-type glioblastomas) harbour TERT mutations. The terms now in use in this category are:

- Oligodendroglioma WHO grade II, IDHmut & 1p19q co-deleted and NOS
- Anaplastic oligodendroglioma WHO grade III IDHmut & 1p19q co-deleted and NOS
- Oligoastrocytoma WHO grade II, NOS
- Anaplastic Oligoastrocytoma WHO grade III, NOS

Oligoastrocytoma NOS is now only used for tumours which have both astrocytic and oligodendroglial phenotypes and there has been a failure or inability at establishing IDH/ 1p19q status. True oligoastrocytomas with dual genotypes (1p19q codeletion in oligodendroglial regions and ATRX loss or p53 expression in astrocytic regions)[17] are extremely rare and are mostly resolved into either category using molecular evaluation.

Other Astrocytomas

This category includes:

- WHO grade I tumours like pilocytic astrocytoma and subependymal giant cell astrocytoma;
- WHO grade II pleomorphic xanthoastrocytomas and
- WHO grade III anaplastic pleomorphic xanthoastrocytomas (PXA III).

Pilomyxoid astrocytomas were previously given a WHO grade II compared with pilocytic astrocytomas, but because of the genetic similarities between the two entities, it is uncertain whether the worse prognosis in pilomyxoid astrocytomas is related to their hypothalamic/chiasmatic location. Therefore pilomyxoid astrocytomas are not assigned a WHO grade within the 2016 classification.[7] Anaplastic pleomorphic xanthoastrocytomas WHO grade III are PXAs with 5 or more mitotic figures in 10 high power microscopic fields. Anaplastic PXAs WHO grade III have fewer BRAFV600E mutations than PXA grade IIs and have a worse prognosis.[18]

Meningiomas

Meningiomas are tumours thought to arise from arachnoidal cap cells in the CNS, accounting for 20% of all primary intracranial neoplasms, with an annual incidence of 2 per 100000 population.

Meningioma classification is nearly unchanged from the previous editions, except for clarity regarding prognostic value of brain invasion in meningiomas, the presence of which categorises the meningioma very clearly as an atypical meningioma, WHO grade II.[7] The category remains based upon histological appearance rather than molecular expression and contains the following WHO grade I variants: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte – rich, and metaplastic; WHO grade II variants: chordoid, clear cell and atypical; and the following WHO grade III variants: papillary, rhabdoid and anaplastic.

Peripheral nerve tumours

The previous entities schwannomas, WHO grade I (comprising schwannoma, plexiform schwannoma and cellular schwannoma variants), neurofibromas WHO grade I (comprising neurofibroma, atypical neurofibroma and plexiform neurofibroma variants), and perineurinomas WHO grade I have been retained. Melanotic schwannoma was a schwannoma variant, but has been recognised as a separate entity due to evidence of potential for malignant transformation in up to 10% of patients:[20] to avoid mis-prognostication, these tumours have not

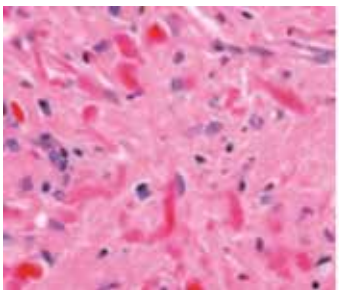


Figure 11: Pilocytic astrocytoma WHO grade I.

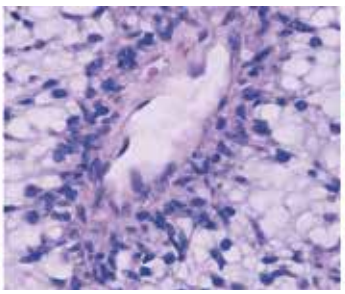


Figure 12: Pilomyxoid astrocytoma.

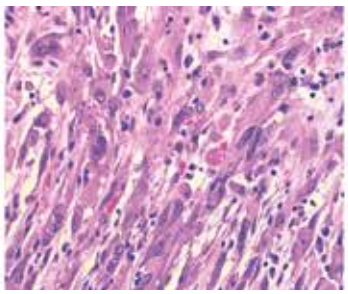


Figure 13: Pleomorphic xanthoastrocytoma WHO grade II.

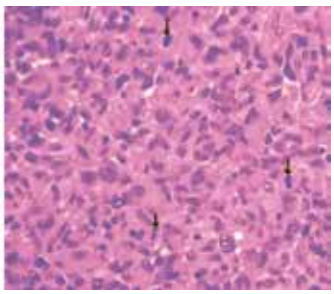


Figure 14: Anaplastic pleomorphic Xanthoastrocytoma WHO grade III.

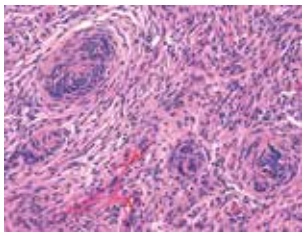


Figure 15: WHO grade I meningioma.

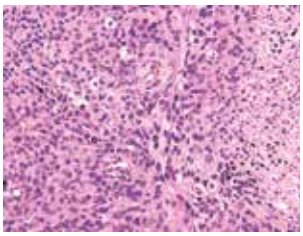


Figure 16: Atypical meningioma, WHO grade II.

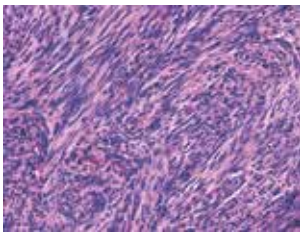


Figure 17: Anaplastic meningioma, WHO grade III.

received any grading. Hybrid nerve sheath tumours, WHO grade I, another new entity, are tumours that show a combined schwannoma, neurofibroma and perineurinoma pattern. Malignant peripheral nerve sheath tumours (MPNST) traditionally had grades II, III and IV and this has been changed to epithelioid MPNST and MPNST with perineurial differentiation instead.[21] Epithelioid MPNSTs show a multilobulated appearance and strong S100 protein positivity. Loss of INI1 expression (67% cases)[22] and rare BRAFV600E mutations raise the possibility of alternate, targeted treatment in these commonly excised, less chemosensitive tumours.[23]

Conclusion

The 2016 molecular WHO classification reflects the recent giant leaps in the understanding of the genetics of brain tumours and hopefully heralds an era of better defined clinical trials and personalised therapeutic options for brain tumour patients. It has not changed the surgical approach to most tumours in the CNS, which still hinges on either a diagnostic biopsy or maximal safe resection. The most important outcome of the new classification has been to highlight molecular targets for novel adjunctive treatments aiming to improve prognosis and survival. It has highlighted the fact that prognostic and survival figures previously estimated for CNS tumours might not be entirely accurate, and there needs to be a paradigm shift in the way we advise our patients about these 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 neuroscience clinicians stay abreast of these developments and work in a multidisciplinary team including neuropathologists, oncologists and neuroradiologists to conduct an informed, up to date practice.

List of abbreviations:

IDH: Isocitrate Dehydrogenase
TP53: Tumour protein (gene) 53
ATRX: Alpha-Thalassemia/ Mental retardation X-linked/ Transcriptional regulator
TERT: Telomerase reverse transcriptase
BRAF: proto-oncogene B-raf/ v-Raf murine sarcoma viral oncogene homolog B
INI1: Integrase Interactor 1

REFERENCES

1. Virchow R. *Die Krankhaften Geschwulste.* Hirschwald 1863-67, Berlin. 1863;
2. Bailey P CH. *A classification of tumors of the glioma group on a histogenetic basis with a correlation study of prognosis.* Lippincott, Philadelphia. 1926;
3. Kernohan JW, Mabon RF, Svien HJ AA. *A simplified classification of the gliomas. Symposium on a new simplified concept of gliomas.* Mayo Clin Proc 71–75. 1949;
4. Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P. *Grading of astrocytomas. A simple and reproducible method.* Cancer [Internet]. 1988 Nov 15;62(10):2152–65.
5. Louis DN. *The next step in brain tumor classification: "Let us now praise famous men"… or molecules?* Acta Neuropathol [Internet]. 2012 Dec 15;124(6):761–2.
6. Louis DN, Ohgaki H, Wiestler OD CW. *World Health Organization Histological Classification of Tumours of the Central Nervous System.* International Agency for Research on Cancer, France. 2016.
7. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK ED, Figarella-Branger D, Reifenberger G von DA. *WHO classification and grading of tumours of the central nervous system.* IARC Press Int Agency Res Cancer, Lyon. 2016;
8. Ohgaki H, Kleihues P. *The definition of primary and secondary glioblastoma.* Clin Cancer Res [Internet]. 2013 Feb 15;19(4):764–72.
9. Kurian KM, Haynes HR, Crosby C, Hopkins K, Williams M. *IDH mutation analysis in gliomas as a diagnostic and prognostic biomarker.* Br J Neurosurg [Internet]. 2013;27(August):1–4.
10. Dang L, Yen K, Attar EC. *IDH mutations in cancer and progress toward development of targeted therapeutics.* Ann Oncol [Internet]. 2016 Apr 19;27(4):599–608.
11. Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK. *Epithelioid GBMs show a high percentage of BRAF V600E mutation.* Am J Surg Pathol [Internet]. 2013 May;37(5):685–98.
12. Perry A, Miller CR, Gujrati M, Scheithauer BW, Zambrano SC, Jost SC, et al. *Malignant gliomas with primitive neuroectodermal tumor-like components: a clinicopathologic and genetic study of 53 cases.* Brain Pathol [Internet]. 2009 Jan;19(1):81–90.
13. Herrlinger U, Jones DTW, Glas M, Hattingen E, Gramatzki D, Stuplich M, et al. *Gliomatosis cerebri: no evidence for a separate brain tumor entity.* Acta Neuropathol [Internet]. 2016 Feb 22;131(2):309–19.
14. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. *Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas.* Acta Neuropathol [Internet]. 2010 Dec 19;120(6):707–18.
15. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RGW, Aldape KD, Yung WKA, Salama SR, et al. *Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas.* N Engl J Med [Internet]. 2015 Jun 25;372(26):2481–98.
16. McNamara MG, Jiang H, Lim-Fat MJ, Sahebjam S, Kiehl T-R, Karamchandani J, et al. *Treatment Outcomes in 1p19q Co-deleted/Partially Deleted Gliomas.* Can J Neurol Sci / J Can des Sci Neurol [Internet]. 2017 May 9;44(03):288–94.
17. Huse JT, Diamond EL, Wang L, Rosenblum MK. *Mixed glioma with molecular features of composite oligodendroglioma and astrocytoma: a true "oligoastrocytoma"?* Acta Neuropathol [Internet]. 2015 Jan 31;129(1):151–3.
18. Ida CM, Rodriguez FJ, Burger PC, Caron AA, Jenkins SM S, GM, Aranguren DL, Lachance DH GC. *Pleomorphic xanthoastrocytoma: natural history and long-term follow- up.* Brain Pathol. 2015;(25):575–586.
19. Saraf S, McCarthy BJ, Villano JL. *Update on meningiomas.* Oncologist [Internet]. 2011;16(11):1604–13.
20. Carney JA. *Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome.* Am J Surg Pathol [Internet]. 1990 Mar;14(3):206–22.
21. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. *The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary.* Acta Neuropathol [Internet]. 2016 Jun 9;131(6):803–20.
22. Jo VY, Fletcher CDM. *Epithelioid malignant peripheral nerve sheath tumor: clinicopathologic analysis of 63 cases.* Am J Surg Pathol [Internet]. 2015 May;39(5):673–82.
23. Rekhi B, Kosemehmetoglu K, Tezel GG, Dervisoglu S. *Clinicopathologic features and immunohistochemical spectrum of 11 cases of epithelioid malignant peripheral nerve sheath tumors, including INI1/SMARCB1 results and BRAF V600E analysis.* APMIS [Internet]. 2017 Apr 27

Table 2: Histological grades of meningiomas with potential recurrence rates[19]

WHO grade	Frequency	Pathologic features	Histologies	Recurrence rates
Grade I	80%-90%	Pleomorphic; occasional mitotic figures; lacks criteria of anaplastic or atypical meningiomas	Meningothelial, psammomatous, secretory, fibroblastic, angiomatous, lymphoplasmacyte rich, transitional, microcytic, metaplastic	7%-20%
Grade II	≥5%-50%	≥4 mitotic figures per 10 high-power fields; three of the following: (a) increased cellularity, (b) small cells with high N:C ratio, (c) prominent nucleoli, (d) sheet-like growth, (e) necrosis; or brain invasion	Clear cell, chordoid, atypical	30%-40%
Grade III	1%-3%	20 mitotic figures per 10 high-power fields or frank anaplastic features	Papillary, rhabdoid, anaplastic	50%-80%

Neurocritical Care Management of the Neurosurgical Patient

This book in its first edition is a novel concept, as a collaborative approach between neurosurgeons, neurologists, physicians, neuro-anaesthetists and neuro-interventionalists. It aims to facilitate mutual understanding of the various specialists' contribution to patient care in the settings of neurocritical care and the neurosurgical operating theatre.

The book is divided into 6 sections. Section 1 reviews core anaesthetic principles: sections 2-5 concentrate on different neurosurgical procedures and sequentially describe neuroanatomy, technical steps of the procedures, peri-operative considerations, anaesthetic choices, post-operative complications and post-operative management for each procedure. Section 6 deals exclusively with potential ICU complications after neurosurgery.

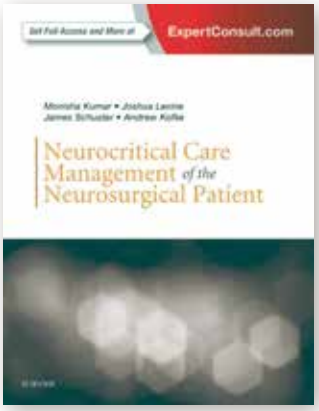
Section 1 (Neuroanaesthesia and Perioperative care) is the weakest section of an otherwise very well edited book. Billed as an outline of core principles in Neuroanaesthesia, it comes across as rather cursory. The "Clinical Pearls" offered seem commonplace. But, perhaps a comprehensive review was beyond the scope of this volume.

From then on, however, matters improve vastly. Sections 2-5 concentrate on different craniotomies (for vascular, oncologic, epilepsy, functional and trauma neurosurgery as well as radiosurgery), spinal surgery, endovascular neurosurgery and special procedures. These chapters are well structured following a consistent outline, offering great clarity. Throughout the book, illustrations are well chosen to underline points made in the text and are of excellent quality with accurate labelling. Some of these illustrations are reproduced from such gold-standard books as Netter's Atlas of Neuroscience and other well-known neurosurgical textbooks. Every chapter has "Key concept" boxes which give a useful overview, although the "Clinical Pearls" refer to rather basic points, rather than sparkling wisdom to those with some prior knowledge. The reference lists are exhaustive and up-to-date, enabling targeted further reading if desired.

Three chapters stand out as being particularly well written: (1) Pituitary Surgery for its in-depth discussion of peri-operative considerations and post-operative management, (2) Trauma Neurosurgery for referencing up-to-date trials such as RescueICP and (3) Spinal Trauma for emphasising the importance of early prevention of sequelae of spinal cord injuries. The only slight criticism of this part of the book would be that the text is occasionally somewhat dogmatic, for instance on the indications of ICP monitoring or on stating the absolute preference for a left-sided approach in anterior cervical discectomy.

Section 6 (Specific Intensive Care Unit Complications) seems at first glance a little short, but does actually provide a good overview of the most commonly encountered neuro-ITU problems.

Overall, the style of writing is engaging and easy to follow, but UK readers of a sensitive disposition might occasionally be put off by American expressions. Although the book is aimed at anaesthetists and neuro-intensivists, neurosurgical trainees will find it a useful resource to prepare for surgical assisting. Their colleagues in medical neurology or rehabilitation might find it useful for reference if attending to a patient as part of an inter-disciplinary team. Priced at $108.99, the book is more expensive than its competitors (although the cost includes access to an ebook for downloading).



Edited by: Monisha Kumar, Joshua Levine, James Schuster and Andrew Kofke.
Published by: Elsevier
Price: £108.99
Pages: 588
ISBN: 978-0323321068

Reviewed by: Heinke Pulhorn, Department of Neurosurgery, Leeds General Infirmary.

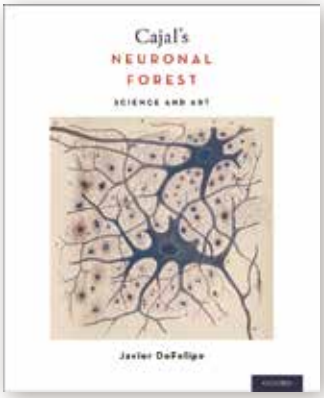
Cajal's Neuronal Forest: Science and Art

This beautiful book would grace any coffee table, and grace a neurologist's coffee table most of all. Its illustrations are truly captivating, and the reproductions of Ramon y Cajal's work can be appreciated all the more because they are presented alongside many other historic drawings, as well as photographs and artworks.

By way of proof that your reviewer read with care, I can comment that I enjoyed seeing Hieronymus Bosch referred to by his Spanish name of El Bosco. I can also confirm that the use of 'shined' as the past tense of 'shine' in the foreword seemed especially inelegant only because it appeared in this most elegant of volumes. In general, however, the text is very impressive in developing the Neuron Doctrine. It provides a comprehensive account, incorporating contributions from Cajal's predecessors. It describes the role of Golgi – an opponent of the Neuron Doctrine (believing instead in the neural network model) despite the fact that his staining method, harnessed by Cajal in particular, was crucial in establishing it.

The latter part of the text, before the gallery of images in the second half of the volume turns to links between neurohistology and the arts. Inevitably this section is less authoritative than the preceding 'history of science': I'm not sure even that an authority on this subject matter exists. The influence of artists on the way Cajal and others presented their work is explored. The specific points seem highly conjectural but the general effect must be real, I think. I would have liked to see slightly more attention to the reverse effect, however. That is, artists being inspired by scientific drawings. And of the paintings where the aesthetic of Cajal's drawings may be discerned, perhaps those of Joan Miró are most convincing.

Would I recommend this book for practice-changing education? Perhaps not. Certainly, I'd keep such a beautiful book well away from any impressionable young relatives you wish to steer away from any career in the neurosciences. Apart from that, it's great.



Author: Javier deFelipe
Publisher: OUP
Price: £52.00
Pages: 484
ISBN: 978-0190842833

Reviewed by: Rhys Davies, Consultant Neurologist, The Walton Centre, Liverpool.

Falls as a result of being on Z-drugs for insomnia

Zheyu Xu
MB BChir, FRACP (Australia), is a Movement Disorders Neurologist based at the National Neuroscience Institute, Singapore and is currently a visiting Clinical and Research Fellow in the areas of Movement Disorders & Sleep Disorders at the University of Newcastle and Regional Sleep Service at the Freeman Hospital, UK.

Kirstie Anderson
BMedSci, MBBS, MRCP, Dphil, is a Consultant Neurologist and Honorary Senior Lecturer specialising in sleep disorders. She has interests in the relationship between sleep and mental health and sleep as a biomarker of normal and abnormal ageing.
www.neurone.org.uk/sleep-resources

Correspondence to:
Kirstie Anderson,
Newcastle Regional Sleep Service,
Freeman Hospital,
Newcastle,
NE7 7DN.
Kirstie.Anderson@nuth.nhs.uk

Conflict of interest statement: None declared.
Provenance and peer review: Submitted and externally reviewed.

Date submitted: 23/2/18
Date submitted after peer review: 15/5/18
Acceptance date: 22/5/18

To cite: Xu Z, Anderson K. ACNR 2018;17(4):10-12

Key take home messages:

- Cognitive behaviour therapy is the recommended first line treatment for insomnia.
- Should Z-drugs be instead used for treatment of insomnia, treatment should be at the lowest dose and for the shortest period of time, typically 14 days.
- Recently published meta-analyses have consistently shown that Z-drug use is associated with an increased risk of falls-related injury with estimates ranging from OR 1.63 to RR 1.92.
- Zolpidem is associated with an increased risk of falls-related injury. Further studies are necessary to confirm if differential falls risk is associated with specific Z-drugs.
- Z-drug use appears to be associated with an excess of falls-related injury, even after correcting for comorbid insomnia.

Abstract
The widespread use of non-benzodiazepine receptor agonists ('Z-drugs') for the treatment of chronic insomnia persists, particularly in the elderly. Recently published meta-analyses have consistently shown that Z-drugs are associated with an increased risk of falls-related injury, which have a dose and time-dependent relationship similar to conventional benzodiazepines. Although insomnia itself can increase falls risk, there is some evidence to show that Z-drugs use results in an excess risk of falls independent of insomnia.

Although cognitive behavioural therapy is recommended as first-line therapy for insomnia, the widespread use of hypnotics persists, particularly in the elderly population. The non-benzodiazepine receptor agonists, known collectively as 'Z-Drugs', reduce sleep onset latency with a relatively preserved sleep architecture. However, the clinical effectiveness of the Z-drugs for the treatment of insomnia is modest at best. Polysomnography studies have shown that Z drugs reduce time to fall asleep by an average of 22 minutes; but do not improve other aspects of sleep such as number of awakenings, total sleep time, and subjective sleep quality.[1]

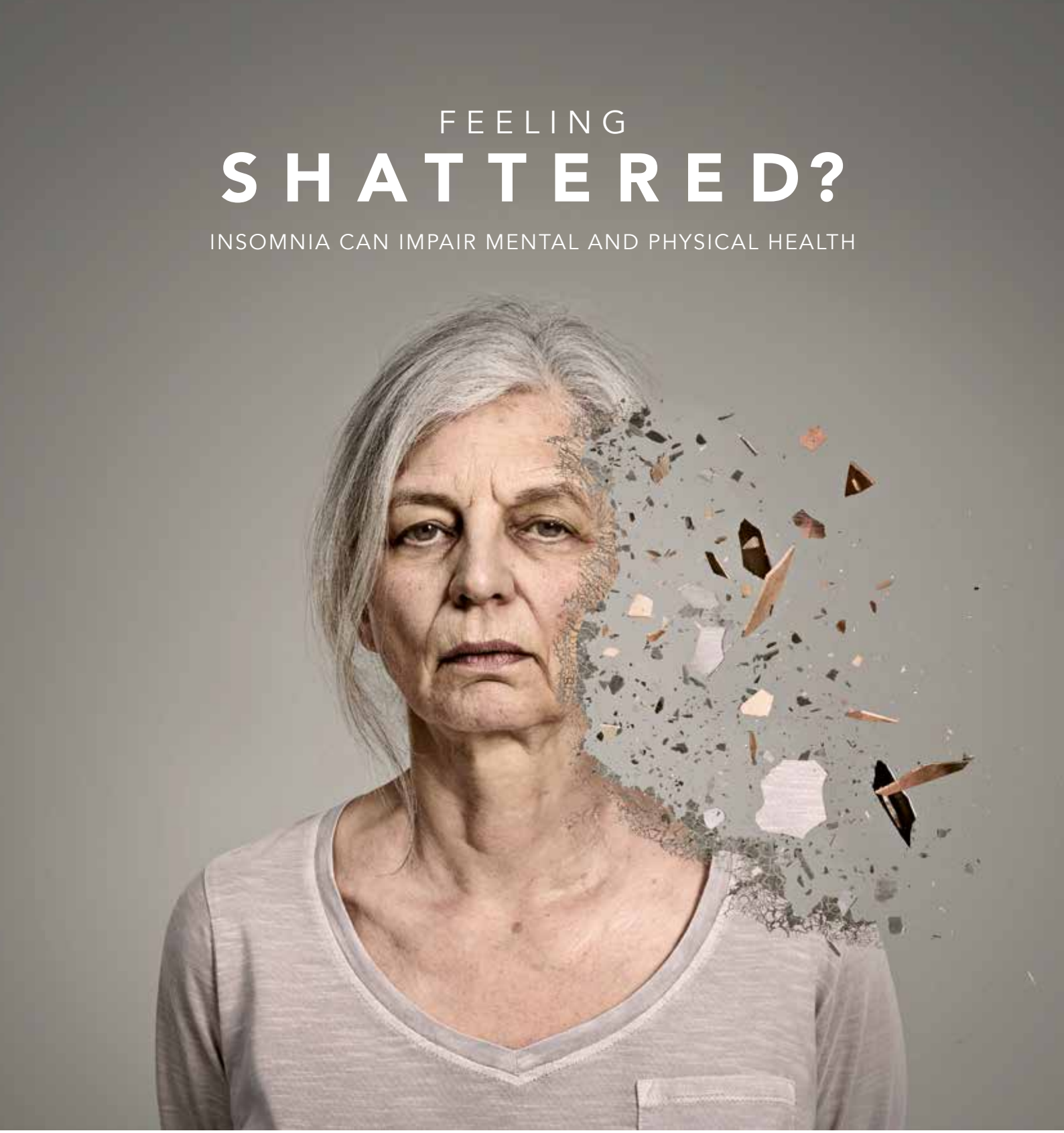
The Z-drugs have a shorter half-life (1-7 hours) compared to conventional benzodiazepines and have been promoted as safer hypnotics with less abuse potential. Early studies on zolpidem performed in mice up to 30 days and controlled trials in humans evaluating intermittent zolpidem use up to 10 weeks have suggested a lower likelihood of tolerance and physical dependence with repeated Z-drug use.[2,3] Although there is limited direct evidence of the risks of dependency in Z-drug use, evidence from studies investigating patient Z-drug use and prescribing patterns in the naturalistic setting suggest a similar adverse profile and propensity for addiction. In the elderly, addiction was observed in 51.8% of zolpidem users and 29.6% of zopliclone users, which was comparable to the addiction rate of 35-40% seen with bromazepam and lorazepam use.[4] In Norway, Z-drug prescriptions in the elderly renewed for repeat use comprised two-thirds of all Z-drug prescriptions, with more than half of prescriptions issued as large quantity prescriptions exceeding 50 tablets. Furthermore, Z-drug prescriptions have increased in parallel with a decrease in benzodiazepine prescribing in the past decade, particularly in the elderly population.[5] The American Geriatrics Society now recommends that Z-drugs not be prescribed beyond 90 days.[6] The NICE guidelines recommend all hypnotics are prescribed at the lowest dose and for the shortest period of time, typically fourteen days.[7] However, there is no data from randomised controlled trials to support fourteen days as a specific time period for Z-drug use.

Z drugs enhance the pharmacological action of GABA receptors in the CNS with a side effect profile similar to benzodiazepines; impairing cognition, gait and balance leading to an increased risk of falls. The elderly are particularly susceptible due to age-related alterations in the pharmacokinetics and pharmacodynamics. Accumulating medical co-morbidities and polypharmacy further increase the risks of falls, with sedative and anticholinergic medications particularly implicated. The English Longitudinal Study of Ageing showed that polypharmacy in the elderly with greater or equal than 10 drugs used was associated with a substantially 50% higher rate of falls over a two-year period. However, an increased falls risk was also seen at lower levels of polypharmacy with the use of just greater or equal to four drugs resulting in an increased falls risk by 21%.[8] Additional Z-drug use thus contributes to further falls risk in an already susceptible patient group. Single test doses of zopiclone administered to healthy elderly subjects result in dose-dependent impairment on postural stability and sway.[9] Zolpidem has been studied in the elderly in a small randomised placebo-control trial to assess balance and cognition during nocturnal awakening two hours after administration of a test dose and induced clinically significant impairments in balance even at the recommended reduced dose of 5mg.[10] Importantly, persistent impairments in balance were also observed 30

FEELING

SHATTERED?

INSOMNIA CAN IMPAIR MENTAL AND PHYSICAL HEALTH



"For people over 55 years of age with persistent insomnia, consider treatment with a modified-release melatonin." - NICE CKS[1]

References and prescribing information can be found overleaf

circadin®

Prolonged-release melatonin

Good nights... and good days

minutes after morning awakening. Tolerance to the cognitive and motor impairment related to Z-drugs may not occur even with chronic use.

The association between benzodiazepine use and increased risk of falls and fractures is well-established; with an often quoted meta-analysis suggesting that adverse outcomes related to benzodiazepine use outweighs the small benefits obtained: in this study, the number needed to treat for improved sleep was 13 as compared to the number needed to cause harm of only 6.[11] Z-drugs have been less well studied; however, there has been accumulating evidence that these drugs have a similar adverse profile to benzodiazepines.

The association of Z-drug use with serious falls with consequent hip fractures was first demonstrated in 2001 in a case-control study evaluating Medicare patients aged 65 and above undergoing surgery for hip fracture. Zolpidem was associated with the highest increased risk of hip fracture (AOR 1.95, 95% CI 1.09-3.51) compared to other medications studied including conventional benzodiazepines, antipsychotics and antidepressants which all increased fracture risk but less than zolpidem.[12]

There has since been accumulating evidence of the association between Z-drug use and falls-related fracture. Zolpidem has been the most studied drug with three recent meta-analyses all reporting an increased risk of falls-related injury of similar magnitude: OR 1.63, (95% CI, 1.42-1.87), RR 1.90, (95% CI 1.68 - 2.13) & RR of 1.92 (95% CI, 1.65, 2.24).[13-15] However, when falls were specifically examined as an outcome in a sub-analysis, Z drug use was not associated with a statistically increased falls risk although there was a trend to suggest an increased risk (OR 2.40, 95% CI 0.92, 6.27).[14]

To understand whether particular Z-drugs pose particular risks for falls: Yu studied the Taiwanese population and obtained an AOR of 1.24, 95% CI 1.38-1.89 with all Z-drug use with higher doses increasing risk;[16] a further study showed a differential effect of Z drugs on risk of falls with an increased risk of TBI (OR 1.87, 95% CI 1.56, 2.25) and hip fracture (OR 1.59, 95% CI 1.41- 1.79) with zolpidem but not with eszoplicone and zaleplon. However, the small number of individuals using zaleplon limited definitive conclusions.[17] Further studies are needed to confirm whether there are differential effects with regards to specific Z-drug use; however there looks to be a link between falls-related injury with Z drug use as a class, and in particular zolpidem.

One criticism of these studies is the confounding effect of insomnia and reduced sleep duration. Insomnia alone increases the risk of falls by impairing daytime function and increasing nocturnal awakenings.[18] One large study of elderly nursing home residents found that insomnia but not hypnotic use was associated with a greater risk of subsequent falls. The greatest risk was in those with untreated insomnia.[19] Therefore, treatment of insomnia using hypnotics in the elderly population could prevent falls.[18,20] However, without well conducted RCTs, this argument remains speculative with most evidence suggesting that Z drugs have a dose and time-dependent relationship with falls-related injuries. Treves attempted to correct for co-morbid insomnia by including studies with a control group diagnosed with insomnia. Importantly this still showed an increased, albeit attenuated, risk for fractures with Z drug use (OR 1.28, 95% CI 1.08, 1.53).[14] Longitudinal data from the Health and Retirement Study found that increasing insomnia symptoms predicted subsequent risk of falling in elderly subjects not using sleep medications. However, those prescribed sleep medications still had a consistently higher falls risk independent of insomnia symptoms compared to subjects not using sleep medications.[21]

Z-drugs may have their greatest risk when first prescribed. Donnelly showed that short term use of Z drugs (up to 14 days) was associated with the greatest risk of hip fractures (RR = 2.39, 95% CI, CI 1.74-3.29) compared to use beyond 30 days.[13] Z drugs are also associated with an excess risk of falls at night.[22] Thus, current prescribing guidelines that limit prescribing to short-term use of Z drugs may not avoid the adverse outcomes of increased falls.

In summary, recent studies have shown that Z-drugs are associated with an increased risk of falls-related injuries with a dose and time-dependent relationship similar to that observed with conventional benzodiazepines. Zolpidem has been particularly implicated. Prescribing guidelines to restrict chronicity of Z drug use, although well-intentioned, may not avoid the risk of falls-related injuries which tend to occur with initial rather than chronic use. A behavioural therapy should be first line treatment for insomnia where possible, particularly in the elderly population.

REFERENCES

1. Huedo-Medina TB, Kirsch I, Middlemass J, et al. *Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration.* BMJ 2012;345:e8343. https://doi.org/10.1136/bmj.e8343
2. Perrault G, Morel E, Sanger DJ, et al. *Lack of tolerance and physical dependence upon repeated treatment with the novel hypnotic zolpidem.* J Pharmacol Exp Ther 1992;263:298-303. http://jpet.aspetjournals.org/content/263/1/298.long
3. Hajak G, Geisler P. *Experience with zolpidem 'as needed' in primary care settings.* CNS Drugs 2004;18 Suppl 1:35-40; discussion 1, 3-5. https://doi-org.libproxy1.nus.edu.sg/10.2165/00023210-200418001-00007
4. Landreat MG, Vigneau CV, Hardouin JB, et al. *Can we say that seniors are addicted to benzodiazepines?* Subst Use Misuse 2010;45:1988-99. http://doi-org/10.3109/10826081003777568
5. Alessi-Severini S, Bolton JM, Enns MW, et al. *Use of benzodiazepines and related drugs in Manitoba: a population-based study.* CMAJ Open 2014;2:E208-16. http://doi.org/10.9778/cmajo.20130076
6. By the American Geriatrics Society Beers Criteria Update Expert P. *American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.* J Am Geriatr Soc 2015;63:2227-46. http://doi.org/10.1111/jgs.13702
7. Guidelines N. *Insomnia : Managing long term insomnia (>4 weeks)* April 2015. https://cks.nice.org.uk/insomnia#!scenario:1
8. Dhalwani NN, Fahami R, Sathanapally H, et al. *Association between polypharmacy and falls in older adults: a longitudinal study from England.* BMJ Open 2017;7:e016358. http://doi/org/10.1136/bmjopen-2017-016358
9. Mets MA, Volkerts ER, Olivier B, et al. *Effect of hypnotic drugs on body balance and standing steadiness.* Sleep Med Rev 2010;14:259-67. https://doi.org/10.1016/j.smrv.2009.10.008
10. Frey DJ, Ortega JD, Wiseman C, et al. *Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial.* J Am Geriatr Soc 2011;59:73-81. http://doi.org/10.1111/j.1532-5415.2010.03229.x
11. Glass J, Lanctot KL, Herrmann N, et al. *Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits.* BMJ 2005;331:1169. https://doi.org/10.1136/bmj.38623.768588.47
12. Wang PS BR, Glynn RJ, Mogun H, Avorn J. *Zolpidem use and hip fractures in older people.* J Am Geriatr Soc 2001;49:1685-90. http://doi.org/10.1111/j.1532-5415.2001.49280.x
13. Donnelly K, Bracchi R, Hewitt J, et al. *Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis.* PLoS One 2017;12:e0174730. https://doi.org/10.1371/journal.pone.0174730
14. Treves N, Perlman A, Kolenberg Geron L, et al. *Z-drugs and risk for falls and fractures in older adults-a systematic review and meta-analysis.* Age Ageing 2017 Published Online First 2017/10/28 doi:10.1093/ageing/afx167:1-8. https://doi.org/10.1093/ageing/afx167
15. Park SM, Ryu J, Lee DR, et al. *Zolpidem use and risk of fractures: a systematic review and meta-analysis.* Osteoporos Int 2016;27:2935-44. https://doi.org/10.1007/s00198-016-3605-8
16. Yu NW, Chen PJ, Tsai HJ, et al. *Association of benzodiazepine and Z-drug use with the risk of hospitalisation for fall-related injuries among older people: a nationwide nested case-control study in Taiwan.* BMC Geriatr 2017;17:140. https://doi.org/10.1186/s12877-017-0530-4
17. Tom SE, Wickwire EM, Park Y, et al. *Nonbenzodiazepine Sedative Hypnotics and Risk of Fall-Related Injury.* Sleep 2016;39:1009-14. https://doi.org/10.5665/sleep.5742
18. Stone KL, Ensrud KE, Ancoli-Israel S. *Sleep, insomnia and falls in elderly patients.* Sleep Medicine 2008;9:S18-S22. https://doi.org/10.1016/S1389-9457(08)70012-1
19. Avidan AY, Fries BE, James ML, et al. *Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes.* J Am Geriatr Soc 2005;53:955-62. http://doi.org/10.1111/j.1532-5415.2005.53304.x
20. Mahgoub N, Majdak P, Friedman DB, et al. *Insomnia and risk of falling in older adults.* J Neuropsychiatry Clin Neurosci 2012;24:E5-6. http://doi.org/10.1176/appi.neuropsych.11070159
21. Chen TY, Lee S, Buxton OM. *A Greater Extent of Insomnia Symptoms and Physician-Recommended Sleep Medication Use Predict Fall Risk in Community-Dwelling Older Adults.* Sleep 2017;40. https://doi.org/10.1093/sleep/zsx142
22. Bakken MS, Engeland A, Engesaeter LB, et al. *Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study.* Eur J Clin Pharmacol 2014;70:873-80. http://doi.org/10.1007/s00228-014-1684-z

WAKE UP ALERT

AFTER RESTORATIVE SLEEP

CIRCADIN® improves sleep quality, morning alertness and quality of life without impairing balance or cognition.[2,3,4]

circadin®
Prolonged-release melatonin

Good nights... and good days

Circadin® 2mg (prolonged-release melatonin) Tablets
Prescribing Information: Please refer to the Summary of Product Characteristics before prescribing. **Presentation:** Circadin 2mg prolonged-release tablets containing 2mg melatonin. **Indication:** Monotherapy for the short-term treatment of primary insomnia characterised by poor quality sleep in patients aged 55 or over. **Dosage and administration:** 2mg orally once daily, 1-2 hours before bedtime and after food. Swallow whole, do not crush or chew. This dosage may be continued for up to thirteen weeks. **Children and adolescents (<18 years):** Safety and efficacy not yet established. **Contraindications:** Hypersensitivity to the active substance or to any excipients. **Special warnings and precautions for use:** Use caution when administered to patients with renal insufficiency. Not recommended for use in patients with hepatic impairment. Circadin may cause drowsiness, therefore use with caution if the effects of drowsiness are likely to be associated with a risk to safety. Not recommended in patients with autoimmune diseases. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Fertility, pregnancy and lactation:** Circadin use in pregnancy and in women intending to become pregnant is not recommended and breast-feeding is not recommended in women receiving melatonin. **Driving:** Circadin has moderate influence on the ability to drive and use machines. **Interactions:** Fluvoxamine should be avoided. Caution should be used in patients on 5- or 8-methoxypsoralen (5- and 8-MOP), cimetidine and oestrogens. Cigarette smoking may decrease melatonin levels. CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure. CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced melatonin exposure. Alcohol should not be taken with Circadin. Sedative properties of benzodiazepines and non-benzodiazepine hypnotics may be enhanced. **Undesirable effects:** In clinical trials the rate of patients with adverse events per 100 patient weeks was higher for Placebo than Circadin (5.743 placebo vs. 3.013 Circadin). There are no *very common* (≥1/10) or *common* (≥1/100 to <1/10) adverse reactions. *Uncommon* (≥1/1,000 to <1/100) adverse reactions include hypertension, chest pain, migraine, headache, irritability, abnormal dreams, nightmares, dermatitis, menopausal symptoms, abdominal pain, abnormal liver function test and asthenia. *Rare* (≥1/10,000 to <1/1,000) adverse reactions include loss of consciousness, angina, palpitations, depression, visual impairment, disorientation, vertigo, haematuria, leukopenia, thrombocytopenia and abnormal laboratory test. Prescribers should consult the full Summary of Product Characteristics for further information on adverse reactions. **Legal category:** POM. **Packs and Prices:** Circadin 2mg, 30 tablets, £15.39. **Marketing Authorisation number:** EU/1/07/392/003. **Marketing Authorisation holder:** RAD Neurim Pharmaceuticals EEC Limited, One Forbury Square, The Forbury, Reading, Berkshire, RG1 Z3EB. **Further information available from:** Flynn Pharma Ltd. Hertlands House, Primett Road, Stevenage, Hertfordshire SG1 3EE. **Date of last revision of PI:** May 2015.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Flynn Pharma Ltd. Medical Information: Tel 01438 727822.

Information about this product, including adverse reactions, precautions, contraindications and method of use can be found at: www.medicines.org.uk/emc/

References
1. Clinical Knowledge Summary (NICE) http://cks.nice.org.uk/insomnia#!scenario:1 (Accessed October 2016)
2. Wade, A., *et al.* Curr Med Res Opin. 2007; 23 (10) 2597-2605
3. Otmani, S., *et al.* Hum Psychopharmacol Clin Exp. 2008; 28 (8) 693-705
4. Otmani, S., *et al.* Hum Psychopharmacol Clin Exp. 2012; 27 (3) 270-276

Date of preparation: December 2016 UK/Cir/1016/0078

Mentoring – Experience from both sides of the fence

Timothy Rittman
BMBS, BMedSci, PgCertMedEd, MRCP, PhD, is a Neurology Consultant and Clinical Research Associate at Addenbrookes Hospital Cambridge and the University of Cambridge. He trained in Nottingham and completed SpR training in the East of England in April 2018. His research aims to understand progression in atypical parkinsonian disorders using neuroimaging and computational analysis.

Srikirti Kodali
MA, MBBS, is a Core Medical Trainee at Addenbrookes Hospital Cambridge. She trained in Cambridge and London and completed the Academic Foundation Programme in East of England before taking on her current post. She aspires to train as a neurologist.

Correspondence to:
tr332@medschl.cam.ac.uk
sk577@cam.ac.uk

To cite: Ritman T, Kodali S. ACNR 2018;17(4):14-15

We have noticed a pattern among the best, the wisest and the most successful people that talk about their life's work. They always refer to their mentors. These mentors are sometimes well known, sometimes not, but are invariably described as a source of support at a crucial time in the career of the successful speaker. This seems more than simply gratitude to a former employer or colleague; the mentoring relationship has shaped and formed the work of the mentee and often proved invaluable to the success of a particular project or idea. We believe successful mentoring relationships remain relevant to today's trainees.

It is no secret that morale is low among junior doctors for a variety of reasons. Since 2012 the number of doctors continuing in training after their F2 year has declined from 70.7% to 55.7% with many choosing to take a break from the treadmill of medical training, move abroad, or leave medicine completely.[1] There are over 45 Core Medical Trainees at our trust of which 75% knew which speciality they wished to apply to at ST3. The Core Medicine curriculum is designed to attain general medical skills in an acute setting and it is not uncommon for trainees not to work in the speciality they wish to train in. It is therefore essential that trainees feel supported to make an informed choice on their ST3 applications. 90% of CMTs did not have a contact/mentor they could approach for advice about their chosen speciality. After ST3 the challenges continue; a survey of trainees in our NHS Trust revealed increasing symptoms of burnout with increasing seniority of registrars. Mentoring could potentially provide critical support for trainees throughout their career.

Mentoring is defined as the relationship between a 'mentee' and a 'mentor', a more senior colleague who works in the same field and can provide advice and direction. This is distinct from a 'coach' who is a more experienced person who may work in a different field and provides a sounding board, or peer support from colleagues at a similar level of experience. Mentoring can be informal or formal. Informal mentoring refers to the chat snatched at the end of a departmental meeting, or the chance meeting over a cup of coffee at the canteen. Formal mentoring is the arranged form and, though can be organised in groups, more usually happens on a one-to-one basis. There is some evidence to support a beneficial effect of mentoring in staff retention, more motivated and experienced workers and better career outcomes.[2]

The medical academic sphere is more advanced in organising and providing mentoring opportunities. As long ago as 2003 the Association of British Neurologists highlighted mentoring as important for all Clinician Scientists and Clinical Research Fellows.[3] The Academy of Medical Sciences mentoring scheme is particularly well developed with a well funded programme and associated resources.[4]

We were partnered as mentor (TR) and mentee (SK) through the Association of British Neurologists (ABN) mentoring scheme.[5] The scheme is administered by the ABN's Trainees committee and partners Neurology Specialist Registrars with Core Medical Trainees interested in applying for Neurology. In addition, we have both been involved with setting up trainee-led mentoring schemes between senior and junior trainees within the Cambridge University Hospitals Foundation Trust. We describe our experiences below.

Setting up trainee-led mentorship schemes

Mentoring scheme for junior Neurology trainees (TR)

In the East of England Deanery we have organised a mentoring scheme for junior neurology registrars that has been active for 18 months. The process started by surveying the registrars to gauge their views on whether they would want a mentor and, if so, should this be a more senior registrar or a consultant. Around half the registrars would be happy with a more senior registrar, and half would prefer a consultant mentor. Taking the path of least resistance, I started with a scheme partnering junior registrars (ST3-5) with senior registrars (ST 6-7). Roughly 80% of our trainees took up the opportunity to have a mentor.

Creating mentoring pairs can be a tricky task, but essentially requires little more than two columns of names and some time. Each mentor was assigned 2-3 mentees. Where possible I tried to match people by geographical location, career interests and social factors. For example, I tried to match registrars who were both following an academic career path, or those interested in working part time with those already doing so. I gave the first refusal of the mentoring partnership to the mentee, but fortunately nobody refused their assigned mentor. Each pair were provided with basic advice on setting up the mentoring relationship, including a link to the BMA's mentoring website (https://www.bma.org.uk/advice/career/progress-your-career/mentoring) that provides an outline of mentoring and links to other resources. The mentee was then left to organise meetings with their mentor.

Informal feedback has been positive, particularly from those new to the region and the Deanery. We have yet to formally evaluate the scheme, but this is planned for later this year.

Mentoring scheme for Core Medical Trainees (SK)

Based on my experience of being a mentee, I set up the 'HippocraTORs and TEEs club' which catered ST3 transition support. CMTs who expressed an interest in a particular medical speciality were introduced to each other and matched to a choice of consultant, SpR and Academic Clinical Fellow within their chosen speciality. After the initial group meeting trainees were expected to organise future meeting independently. The objectives of the programme were broadly based on ARCP training outcomes but with an added speciality focus in addition to support around applications, interviews and further career progression. Recruitment of mentors was surprising easy within our trust reflecting the high levels of motivation to participate and satisfaction that mentors gain from the process. Initial feedback from both the mentors and mentees was very positive and we plan to expand the model across other trusts in the deanery.

Being a Mentee (SK)

My experience of the ABN mentorship programme has been excellent and I am lucky to have a mentor within the same trust. I got some very useful tips from TR at our first meeting on how to prioritise my various extra-rotational activities that I was involved in at that time. We met a few times thereafter to focus on more specific issues, for example, discussing a neurology case I had encountered on the ward and pursued to submit an abstract for a trainee case presentation competition. A successful local mentor-mentee relationship can be resourceful in multiple ways – it was useful to be directed to educational opportunities within the trust in the form of clinics, department teaching, audits, clinical research projects, etc.

The benefit of the mentoring relationship has been the informality and the flexibility to cater my individual needs and preferences.

Being a mentor (TR)

Through the East of England Neurology Trainee scheme and the Association of British Neurologists scheme I have now met up with 4 mentees over the past 18 months, all very different in their stages of career and intended path. Two of those I have met on only one occasion so far, the other two have been more regular chats. I have found the experience of mentoring immensely rewarding. Firstly, it has been great to get to know these colleagues better. Secondly, there is a sense of satisfaction in helping people avoid the mistakes I have made and take advantage of opportunities they didn't know existed. Thirdly I feel I have been able to give something back to neurology as a specialty, and in particular the East of England training scheme. Discussions have been wide-ranging, from the impact of life events (eg starting a family), to planning an academic career, and starting out on the on-call rota.

Mentoring SK has been a great experience. It has brought to mind the period of uncertainty I went through before gaining a foothold as a neurology registrar. Although her path has been different to mine in many ways, I have the perspective to look back and help her to prioritise the most useful activities and not to be too concerned with those less relevant to her career progression. SK sets the agenda and our conversations have been more of a discussion than me providing endless advice. I have also been able to link SK with other people in the department who can provide help and support on specific issues.

Summary

In conclusion, we believe mentoring is as relevant now, if not more so, as it ever was. A successful mentoring relationship is directed by the mentee and flexible in its commitment and scope. The rewards of mentoring are not limited to the mentee; the mentor and wider organisation also benefit from these very special kind of professional relationships. We have benefited as mentor and mentee from participating in the Association of British Neurologist's mentoring scheme which we highly recommend. We believe that mentorship schemes should be available to all post-graduate trainees and we have demonstrated that trainee-organised mentoring schemes are practical and feasible.

REFERENCES

1 *Training pathways: analysis of the transition from the foundation programme to the next stage of training.* 2017. https://www.gmc-uk.org/Training_pathways_1___FINAL2.pdf_72695703.pdf

2 Allen TD, Eby LT, Poteet ML, et al. *Career Benefits Associated With Mentoring for Proteges: A Meta-Analysis.* J Appl Psychol 2004;89:127–36. doi:10.1037/0021-9010.89.1.127

3 Association of British Neurologists. *Academic Neurology in the United Kingdom: Treats, Opportunities and Recommendations.* 2003.

4 Mentoring Programme | The Academy of Medical Sciences. https://acmedsci.ac.uk/grants-and-schemes/mentoring-and-other-schemes/mentoring-programme (accessed 17 May 2018).

5 Association of British Neurologists. *ABNT Mentoring Programme*. http://www.abnt.org.uk/mentoring.php (accessed 21 May 2018).

Hansen's bacillus

JMS Pearce MD, FRCP
Emeritus Consultant Neurologist, Department of Neurology, Hull Royal Infirmary, UK.

Correspondence to:
J.M.S. Pearce, 304 Beverley Road Anlaby, East Yorks, HU10 7BG, UK.
Email: jms.pearce@me.com

Conflict of Interest statement: None declared.

Date first submitted: 23/1/18
Acceptance date: 4/2/18

To cite: Pearce JMS, ACNR 2018;17(4);16-18

Abstract
Because of its gradually declining incidence many UK physicians rarely encounter leprosy which is thus easily overlooked. Hansen's discovery of mycobacterium leprae, the first identified human bacterial infection, was of crucial importance. He struggled to find acceptance, and arguments about priority of his discovery were rife until his vital role was established in the Leprosy congress in Berlin in 1897.

Leprosy was the first proven instance of a bacterial infection causing a human disease. Its importance cannot be overemphasised, because it was the first direct evidence of the causal role of microorganisms predicted but not proved by the *Germ theory* of the 1800s that stated many diseases are caused by the presence and actions of specific microorganisms. Germ Theory superseded existing theories of disease: divine superstitions, miasma and contagion, and thereby revolutionised the practice of Medicine. The global prevalence has decreased from approximately 600, 000 cases in 2001 to <200,000 in 2015,[1] but under-reporting is likely. It remains a worldwide scourge.[2]

The existence of 'germs', 'microbes', or 'microorganisms' however, had preceded Germ Theory, for in 1676-7, using his first microscope, Antonie van Leeuwenhoek (1632–1723) of Delft, observed tiny organisms — which he called 'animalcules' — but he did not relate them to disease. It was Louis Pasteur (1822-95) and Robert Koch (1843-1910) who showed that microbes caused infectious diseases. Pasteur showed in 1863 that microorganisms caused fermentation of milk and grapes, and the putrefaction of meat. He therefore suggested human disease was caused by the multiplication of germs in the body.[3]

Koch proved that *Bacillus anthracis* that he observed in the tissue of anthrax victims was the cause of anthrax[4] and crucially was transmissible. He extracted this bacterium from a sheep which had died of anthrax, then repeatedly injected generations of mice with it; the mice developed the disease. Koch announced in 1876 that he had proved this bacterium caused *anthrax*. He went on to identify the bacterial causes of tuberculosis (1882), and cholera(1883).

Gerhard Armauer Hansen (1841-1912) worked at St. Jørgen's hospital in Bergen, striving to find the cause of leprosy. Importantly, Hansen's identification of M. leprae preceded Koch's seminal investigations.[5] Leprosy is a chronic mycobacterial infection that affected millions of people, mainly in Brazil, India, and Indonesia.

The *Tuberculoid* or *paucibacillary* type shows well-expressed cell-mediated immunity that controls bacillary multiplication by forming epithelioid-cell granulomas. The *lepromatous* or *multibacillary* type shows cellular anergy towards M. leprae, thus profuse bacillary multiplication. Between these is a continuum, varying from *borderline tuberculoid*, through borderline, to those with little cellular response, *borderline lepromatous*.

Clinical Features

Hansen had observed varied clinical features. Typically there was a variety of skin lesions: a large single well-defined red patch or asymmetrical hypo-pigmented macules, plaques, and nodules, often thickening of the forehead and earlobes, loss of eyebrows, deformity of the nose and loss of the upper incisor teeth. Neuropathy was accompanied by sensory loss and tender, thickened peripheral nerves. It could resolve spontaneously or progress to borderline or lepromatous leprosy with hideous deformities.

Figure 1: Patient ('elephantiasis') at St Jørgen's hospital. (Photo MHSB02924: Lepramuseet St. Jørgens hospital).

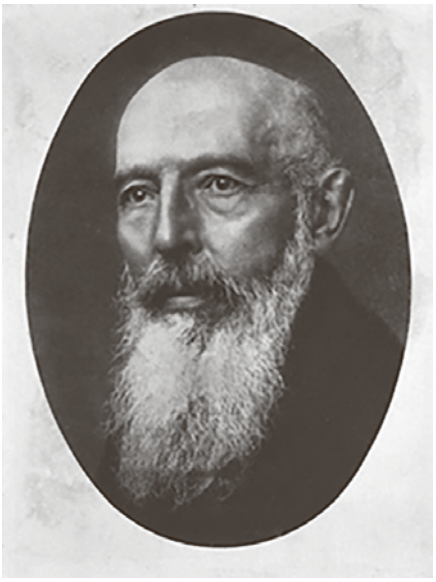


Figure 2: Gerhard Armauer Hansen. 1900s (Photo by Mondadori Portfolio via Getty Images)

Hansen also observed visual impairment or blindness now known to result either from mycobacterial infiltration of the anterior segment of the eye, or from trophic changes caused by damage to trigeminal and facial nerves, resulting in lagophthalmos, deformed eyelids or corneal anaesthesia.

Hansen's bacillus

Hansen was born to a Danish family the eighth of 15 children, at Bergen on July 29, 1841. His father Claus was a merchant who after a crisis went bankrupt. His memoirs show details of his childhood and professional life.[6] He studied Medicine at the University of Christiania (now Oslo), qualifying in 1866. In 1870, he went to Bonn and Vienna to study histopathology. Returning to Bergen in 1868, he was appointed assistant physician to the distinguished Daniel Cornelius Danielssen (1815-1894) at St. Jørgen's hospital for lepers. He searched for the aetiology of leprosy, in blood, then in leprous tissues. It was here that Hansen discovered the causative agent of leprosy, M. lepra, in 1873.[7,8,9] This was three years before Koch identified the anthrax bacillus and nine years before he showed that tubercle bacillus caused human tuberculosis.

The prevalence of leprosy in Bergen was high, estimated at c. 25 per 1,000 population. With Carl Wilhelm Boëck (1808-1875) of Oslo, Danielssen had pioneered the scientific study of leprosy.[10] St. Jørgen's hospital was established in the 14th-century and became a famous leprosy research centre. Danielssen believed leprosy was hereditary, but Hansen suspected it was infectious.

Having observed yellowish granular masses in leprous tissues in 1869, in 1873 he discovered the rod shaped bodies that looked like bacteria in 'lepromata', later identified as M. Leprae. 'Danielssen at first disputed Hansen's evidence of an infectious cause. Hansen read a paper in 1874 to the Medical Society of Christiania, claiming these bodies were the cause of leprosy. It was published in the *Norsk Magazin*

for Laegevid–enskaben, as an 88-page monograph in 1874. However, written in Norwegian, its readership was limited and failed to excite interest in the medical world. We can recognise his scientific caution, for at first he was uncertain whether these rod-shaped bodies were bacteria, perhaps because he failed to culture or stain them adequately:

> There are to be found in every leprous tubercle extirpated from a living individual — and I have examined a great number of them — small staff-like bodies, much resembling bacteria, lying within the cells; not in all, but in many of them. Though unable to discover any difference between these bodies and true bacteria, I will not venture to declare them to be actually identical. Further, while it seems evident that these low forms of organic life [i.e., bacteria] engender some of the most acute infectious diseases, the attributing of the origin of such a chronic disease as leprosy to the apparently same matter must, of course, be attended with still greater doubts. It is worthy of notice, however, that the large brown elements found in all leprous proliferations in advanced stages … bear a striking likeness to bacteria in certain stages of development…"[11]

But after consulting Robert Koch, he improved his techniques and in 1880 did stain the bacilli. However, in 1879, Albert Neisser (discoverer of *Neisseria gonorrhoea*) claimed discovery of the leprosy bacillus, using material he obtained from Hansen during a visit to Bergen. Using superior fuchsin and gentian violet stains, Neisser described the lepra bacilli, their appearance and distribution.[12]

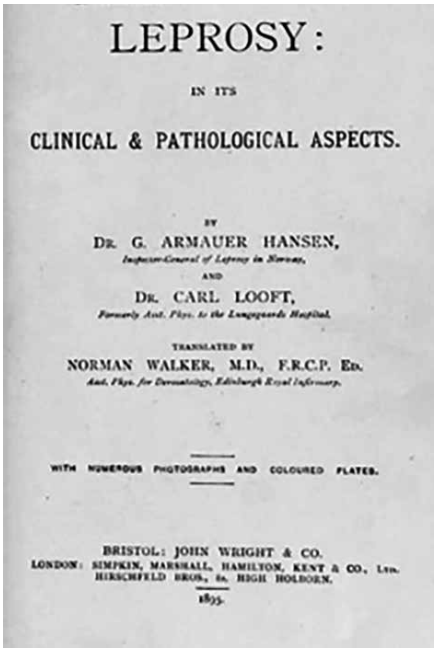
Danielssen however, encouraged Hansen to counter Neisser's claim for priority.[13] An angered Hansen updated his original report to publish new articles simultaneously in English,[11] German, and Norwegian journals in 1880, establishing his priority in the discovery.[14,15]

> I feel myself called upon to announce what I have attained to, up to the present time, in my researches after the same 'contagium,' and, this, partly to assert my priority with reference to this discovery, and partly in order to advance those details in research which I omitted to announce on account of the still uncertain result in my report to the Medical Society of Christiania, 1874, concerning my investigations into the aetiology of leprosy."

However, Neisser later retracted his claim for priority:

> I have never claimed for myself the priority of having been first to see bacteria in leprosy...[16]

Although Hansen had described acid, alcohol resistant bacilli in leprous lesions, he struggled in vain to culture M. Leprae or to satisfy Koch's postulates*. Frustrated, in 1879, he inoculated the eye of a woman with material drawn from a leprous nodule. But because he had failed to obtain informed consent Hansen was found guilty of unethical conduct when tried at Court in Bergen. He lost his position as physician of the Bergen hospitals, but retained his job as leprosy medical officer for the entire country of Norway. Henry Vandyke Carter (a major contributor to Gray's Anatomy, and leprologist in India) visited Hansen's laboratory and vigorously supported him and his conclusions that leprosy was due to an infectious bacillus, in his article *On leprosy and elephantiasis*. (London: Eyre and Spottiswoode,1874). At a Leprosy congress in Berlin (1897) Hansen was finally recognised[17] as the discoverer of the lepra bacilli, the cause of leprosy. Leprosy is often named 'Hansen's disease.'


LEPROSY:

IN ITS

CLINICAL & PATHOLOGICAL ASPECTS.

BY

DR. G. ARMAUER HANSEN,

AND

DR. CARL LOOFT,

TRANSLATED BY

NORMAN WALKER, M.D., F.R.C.P. Ed.

WITH NUMEROUS PHOTOGRAPHS AND COLOURED PLATES.

BRISTOL: JOHN WRIGHT & CO.

LONDON: SIMPKIN, MARSHALL, HAMILTON, KENT & CO., Ltd.

HIRSCHFELD BROS., 61, HIGH HOLBORN.

1895.

Figure 3: Leprosy... Hansen and Looft 1895

Hansen then worked at the Bergen Museum. He wrote extensively and sought to spread Darwin's theory of evolution. He also wrote about whaling and marine life.

In 1873, he married Danielssen's daughter, Stephanie Marie, who died of tuberculosis only months later. It is reported that he suffered with syphilis and died of 'a heart attack' in 1912, aged 71. Hansen was to receive many honours, including the doctorate of the University of Copenhagen. His statue was erected in the gardens of the Bergen Museum eleven years before his death on 13 February, 1912, at which time his ashes were placed in a bronze urn beneath the bust.

Origins of leprosy

The word lepra in Latin was applied to patients, but historically was known as Elephantiasis Grecorum, which in turn replaced the Greek lepra taken from the biblical word tsara'ath. It was often mistranslated as leprosy, though literally it signified any disease with a scaly skin, such as psoriasis, scabies, and syphilis. Before Hansen's discovery, Robley Dunglison, personal physician to Thomas Jefferson, showed the bewildering variety of names in his textbook, The Practice of Medicine:[18]

II ELEPHANTIASIS GRECORUM

SYNON. Lepra tuberculosa, L.Aegyptiaes, L. Alba, L. Hebaeorum, L. leon-tina, L. Mosaica, Tsarath of Moses, Leontiasis, Satyriasis, Lepra, Leuce, Mor-phaea alba, Baras, Vitiligo; Fr. Lèpre tuberculeuse, Elèphantiasis des Grecs, Ladrerie, Tete de veau, Mal rouge de Cayenne; Ger. Weisse oder Mosaiche Aussatz, Knolligre Aussatz.

In the bible, Lepers were 'unclean' and isolated from the community. Their plight is shown in Leviticus (13.2):

> When a man has on the skin of his body a swelling or a scab or a bright spot, and it becomes an infection of leprosy on the skin of his body, then he shall be brought to Aaron the priest or to one of his sons the priests. … All the days wherein the plague shall be in him he shall be defiled; he is unclean: he shall dwell alone; without the camp shall his habitation be.

And in Matthew (8:3):

> And Jesus put forth [his] hand, and touched him, saying, I will; be thou clean. And immediately his leprosy was cleansed.

Leprosaria

Although leprosy is now known not to be highly contagious, since biblical edicts lepers were stigmatised and condemned to a lifetime of monastic isolation, social abhorrence, fear and rejection. In AD 625, the first-known leper hospital in England, was founded at Nottingham (Blyth Leper Hospital). And in 1101 Queen Matilda, wife of Henry I, founded a leper house at St Giles in the Fields, London. Throughout the world leper colonies, leprosaria, sanatoria or asylums were created to isolate sufferers. By 1225 there were around 19,000 in Europe. In medieval England, at least 345 hospitals were wholly or in part for lepers. In 1816 Johan Ernst Welhaven (1775-1828) exposed the shameful living conditions at the 400-year-old St Jørgen's Hospital in Bergen, as a "graveyard for the living." But humane reforms were slow to materialise.

Hansen's second major contribution was to encourage new laws, introduced in Norway in 1877 and in 1885 requiring that lepers be isolated in hospitals to stop them from spreading the disease. This proved effective and was confirmed in 1897 at the First International Leprosy Congress,

The first effective treatment (the sulphone, promin) became available in the 1940s. In 1945, Robert Greenhill Cochrane (1899-1985)

a British leprologist studied sulphonamide derivatives, and was among the first to use dapsone (diaminodiphenyl sulfone) c.1947-9 in leprosy.[19,20]

The search for effective drugs yielded clofazimine and rifampicin in the 1960s and 1970s.[21] Shantaram Yawalkar and his colleagues formulated a multi-disease treatment (MDT), which impeded dapsone-resistant forms.

When the sulphones were introduced as the first effective treatment, many sanatoria and asylums were closed and public attitudes improved. However, new cases have not yet been eliminated. At the end of 2016 the prevalence was 0.23 per 10,000 population with 214,783 new cases (2.9 per 100 000) reported globally.[22]

REFERENCES

1. Fulton N, Anderson LF, Watson JM, et al. *Leprosy in England and Wales 1953–2012: surveillance and challenges in low incidence countries.* BMJ Open 2016;6:e010608. doi: 10.1136/bmjopen-2015-010608.
2. Rodrigues LC, Lockwood DNJ. *Leprosy now: epidemiology, progress, challenges, and research gaps.* Lancet Infect Dis 2011;11:464–70.
3. Pasteur L. *'Recherches sur la putrefaction'*, Comptes Rendus de l'Académie des Sciences 1863;66:1189-94.
4. Koch, R. *Untersuchungen über Bakterien: V. Die Ätiologie der Milzbrand-Krankheit, begründet auf die Entwicklungsgeschichte des Bacillus anthracis.* Cohns Beitrage zur Biologie der Pflanzen 1876;2, no. 2, 277–310.
5. Vogelsang TM. *Gerhard Henrik Armauer Hansen 1841-1912. The discoverer of the leprosy bacillus. His life and his work.* Int J Lepr Other Mycobact Dis. 1978;46:257–332.
6. Larsen O. *Gerhard Henrik Armauer Hansen Seen Through His Own Eyes.* International Journal of Leprosy1973;41(2):208-14.
7. Hansen A. *Indberetning til det Norske medicinske Selskab i Christiania om en med Understøttelse af Selskabet foretagen reise for at anstille Undersøgelser angående Spedalskhedens årsager, tildels du førte sammen med forstander Hartwig.* Norsk Mag Laegevidenskaben 1874;4(Suppl.9):1-88.
8. Irgens LM. *The discovery of the leprosy bacillus.* Tidsskr nor Laegeforen. 2002;122(7):708-9. PMID 11998735.
9. Grzybowski A, Kluxen G and Półtorak K. *Gerhard Henrik Armauer Hansen (1841–1912) – 100 years anniversary tribute.* Acta Ophthalmologica 2014;92:296–300. doi:10.1111/aos.12159.
10. Danielssen DC, Boeck CW. *Om Spedalskhed Bergen, Christiania 1847, translated into French as "Traité de la Spedalskhed ou Elephanthiasis des Grecs"* (Paris 1848).
11. Hansen GA. *On the Etiology of Leprosy.* Br Foreign Medico-chirurgical Rev 1875;55:459-89.
12. Neisser A. *Zur Aetiologie del' Lepra.* Breslauer Arzl. Zeitschr 1879;200-202;214-15. Cited by: Fite GL, Wade HW. (ref 13).
13. Kobro I. Gerhard Henrik *Armauer Hansen.* Annals of Med History. 1925;7:127–32.
14. Fite GL, Wade HW. *The contribution of Neisser to the establishment of the Hansen bacillus as the etiologic agent of leprosy and the so-called Hansen-Neisser controversy.* Int J Lepr 1955;23:418-28.
15. Marmor MF. *The ophthalmic trials of G. H. A. Hansen.* Surv Ophthalmol 2002;3:275-87 .
16. Neisser, A. *Weitere Beitrage zur Aetiologie del' Lepra.* Vorliiufige Mitteilung.. Archiv f. pathol. Anat. 1881;84:514. https://doi.org/10.1007/BF01937671.
17. Hansen GHA, Looft C. *Leprosy: in its clinical and pathological aspects.* Bristol: J. Wright; 1895.
18. Hunglison R. *The Practice of Medicine; Or, A Treatise on Special Pathology and therapeutics*, Volume 2, Lea & Blanchard, 1842, Fig 4:
19. Zhu YI, Stiller MJ et al. *Dapsone and sulfones in dermatology: overview and update.* Journal of the American Academy of Dermatology 2001;45(3):420-34.
20. Greenwood D. *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph.* Oxford, OUP 2008. Pp. 196-8.
21. Rees RJ, Pearson JM, Waters MF; Pearson; Waters. *Experimental and Clinical Studies on Rifampicin in Treatment of Leprosy.* Br Med J 1970;688(1):89-92.
22. *WHO Global Leprosy Programme – Epidemiology.* 2017. www.searo.who.int/entity/global_leprosy_programme/epidemiology/en/

* *1. A specific microorganism is always associated with a given disease. 2. The microorganism can be isolated from the diseased animal and grown in pure culture. 3. The cultured microorganism will cause disease when transferred to a healthy animal. 4. The same microorganism can be isolated from the newly infected animal.*

Acquired brain injury – life after rehabilitation and 'never saying never'

Mark Smith
is Ryan's father and is a serving paramedic with EMAS.

Gemma Kelly
is a Physiotherapist and Researcher at The Children's Trust, and worked with Ryan during his time at the charity.

Provenance and peer review:
Invited and internally reviewed.

Conflict of interest statement:
None declared

To cite: Smith M, Kelly G. ACNR 2018;17(4);19-20

Ryan Smith was hit by a van as he was cycling to work in 2013, he was 16 years old. Defying medics, Ryan survived, but with a severe and life changing brain injury. Here Ryan's father Mark, a serving paramedic with EMAS, talks about the value of personalising care when working with someone with brain injury.

Ryan remained in a coma for 123 days, and we were told that he might not survive. Yet four months after the accident Ryan opened his eyes. I asked him to say hello and he took a deep breath and said, 'hello'. After jumping around for 10 minutes I composed myself. I thought I'd push my luck and asked him to say 'dad'. He did. Then he said 'Mum'. From that day on we haven't looked back.

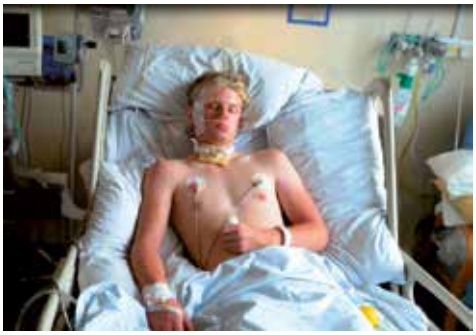
I firmly believe that during those dark early days, the family clutching to hope and believing he could pull through kept Ryan's spirit alive. Despite all the negative prognoses we received, we never stopped whispering in his ear that he could win the battle. They say hearing is the last sense to leave, so we clung onto hope and kept encouraging Ryan to heal. I know his brain was scrambled at the time but the family truly believe he could sense our presence.

After hospital, Ryan received nine months of intensive rehabilitation at The Children's Trust. We stayed with him, despite the 400-mile round trip to be there, which meant we were able to support and encourage him during rehabilitation sessions. It also meant we were able to learn the skills we needed to be able to care for him. The 24/7 care we received at the charity supported Ryan to learn how to eat orally again instead of through a tube into his stomach, and developed his speech. By April 2014, Ryan stood unaided.

Intensive rehabilitation made a crucial difference, not only to how Ryan is today but also to how the family copes day-to-day. The rehab gave us back more of our boy than we ever hoped for. Just as importantly, advice given to the family with what to expect now and in the future was a component that should not be overlooked. Moving home after residential rehabilitation can be hugely overwhelming – how will you cope, what if you can't cope? You're acutely aware that life isn't the same but looking ahead is extremely frightening and painful. A prepared family (as ever can be) helps massively with transition back to home life.

Now, Ryan is studying media full-time at a mainstream college, and is loving the experience. It's not without tribulations and tired days but for the most part he is very upbeat. The support staff have been fantastic with Ryan and have really got to grips with Ryan's ways and needs.

Positive but realistic support is crucial. Professionals that take an open-minded, let's-try-it-approach, build Ryan's determination and zest for life and that's important. While it's important to live in the present, everyone wants to have dreams, goals and ambitions.



Professionals that learn and work with Ryan's traits see the best results, especially when he's involved in decision making. Ryan's filter has diminished and his language can be colourful, so it is important to learn what makes him tick and never take insults personally. He will always apologise post-rant. It's also important to have an understanding of control measures. Giving Ryan space for a minute or so usually does the trick, his outbursts disappear as quickly as they start.

Brain injury often means that someone can struggle with concentration levels, so it's crucial that professionals are mindful of fatigue. Any outbursts usually coincide with tiredness. At the same time, it's also crucial to be firm yet fair when these events occur in order to regain his attention.

An understanding of Ryan's interests and needs is always conducive to a positive outcome. Predominantly Ryan is both determined and witty, often making the family smile with his humour. He will do the same for any professional if a little time is taken to 'learn' him.

There have been more recent challenges to overcome. A right handed tremor has affected pen to paper exercises severely, so Ryan completes his coursework with a computer. Ryan's short term memory is also grossly effected, so computer generated work can be saved and valuable effort is not lost. The tremor is possibly the most frustrating aspect for Ryan at the moment as he requires more assistance at meal times to reduce spillage. Ryan is still a very proud young man, and fashion and appearance are high on his priorities, so fear of dropping food has severely dented his confidence when eating and drinking. Efforts to reduce the tremor are ongoing, frustratingly fruitless to date.

Physically, Ryan still has left sided hemiplegia so is totally reliant on assistance with all transfers. Yet he always helps as much as he can with his strong right side. On the plus side Ryan now uses a power chair and can self-propel around college and home which is proving to be a wonderful mode of transport and independence.

The future is looked upon with great trepidation and, to be honest, fear. Ryan has dreams of an independent life. Because of his injuries the family are less sure this is achievable. We have always tried to keep the glass half full, always

remained cautiously optimistic for a positive future for Ryan. We cannot see past college at present and have received very little guidance as to what is out there for Ryan's journey post-college. Despite regular meetings with local authorities as to what is available for Ryan to help him continue to evolve and move forward with his life, we have not really had any positive assistance. We also remain realistic with how Ryan's short term memory loss will severely affect his chances of employment. Although we never say never.

Ryan is a fantastic young man who has adapted amazingly, smiles for the majority and is incredibly resilient. We are extremely proud of him.

Gemma Kelly is a Physiotherapist and Researcher at The Children's Trust, and worked with Ryan during his time at the charity

Every child and family has a different experience of brain injury, and require an individualised approach to their rehabilitation which takes into account their unique needs, strengths and hopes. As Mark highlights, one of the key aspects of rehabilitation is working with families to enable them to return to their family life, and to cope with the challenges that they may face in the future. As professionals, we learn from every family that we work with, and understanding the real experiences, both positive and negative, can help us to better support every family we work with.

Last year The Children's Trust, which has recently been rated Outstanding by the Care Quality Commission, held its first national paediatric brain injury conference. The programme was headlined from a patient and parent perspective. Ryan and his father Mark gave important insights into their experience of residential rehabilitation following Ryan's brain injury. They presented a personal and very honest account of their placement at The Children's Trust and stressed the value of family support from a variety of sources including tea around the table with other families, the nursing staff in addition to the formal support offered by the psychosocial and therapy teams. Their experiences stimulated a prolonged question and answer session from delegates who included neurologists, doctors, nurses, and lawyers.

The Rubik's Cube of Childhood Brain Injury is the second paediatric conference hosted by The Children's Trust. Taking place on Wednesday 20 June 2018 at The Royal Society of Medicine in London, the event will look at the complexities, connections and challenges of acquired brain injury in children and young people.

Speakers include international neuroscientist, clinician and author, Dr Lucia Braga, The SARAH Network; Mr Simon Stapleton, Consultant Neurosurgeon, St. George's Hospital; Dr Vijeya Ganesan, Senior Lecturer in Paediatric Neurology and Honorary Consultant Paediatric Neurologist, Great Ormond Street Hospital, and many more.

For more information see www.thechildrenstrust.org.uk/conference

Neurovascular Disorders: Latest treatments and best practice

Conference details: April 16th, 2018, London, UK. ***Report by:*** Ms Aida Kafai Golahmadi, Medical Student, Imperial College London and Mr Patrick Grover, Fellow in Neurovascular Surgery, National Hospital for Neurology and Neurosurgery. ***Conflict of interest statement:*** None declared

This meeting, held at the Royal Society of Medicine (RSM) in London, sponsored by the Brain and Spine Foundation and Clinical Neurosciences Section of the RSM was chaired by Professor Peter Hutchinson, President of the Section, and comprised updates on the latest treatments and best practice, with talks giving perspective on all aspects of the patient's journey, from diagnosis to acute management and long term rehabilitation. Particular emphasis was placed on a holistic discussion of neurovascular disorders, with talks from surgeons, radiologists, physicians, therapists and neuropsychologists.

Mr Trivedi from Cambridge began with the pathophysiology of neurovascular disorders, focusing on acute ischemic stroke. He advised that we have to act faster and suggested to change the term 'stroke' to 'brain attack'.

He discussed the concept of ischemic penumbra, that portion of the ischemic territory that could be saved from progressing to irreversible infarction if re-perfused in a timely manner (within 60 minutes or less from the time of arrival). Mechanical thrombectomy (MT) can do so with a number needed to treat of less than 3 for an improved functional outcome, which is unmatched by any previous therapy in stroke medicine. The challenge now is to implement accessible and safe MT services.

Mr Kitchen, President-elect of the Society of British Neurological Surgeons, followed with a talk on cavernomas. The highlight of this session was the uncertainty that still persists with regards to which patients should be treated promptly and which ones we should "watch and wait". The imminent need for accurate estimates of haemorrhage risk in the natural untreated cerebral cavernous malformation led to the development of a list of unanswered research questions by the James Lind Alliance, a partnership between clinicians and patients. At the top of their research priorities are understanding whether treatment (with microsurgical excision or stereotactic neurosurgery) improves outcomes, and identifying the risk factors that predispose to bleeding. In the absence of Class I evidence, the best current treatment is to counsel the patients and explain to them the uncertainties of surgical and conservative managements.

Mr Nelson, previous SBNS President, discussed the role of bypass in the management of complex intracranial aneurysms. 20 years ago he predicted the standard of care would shift towards endovascular coil embolisation rather than microsurgical clipping, but this means often the most complex cases require surgical management. He presented his extensive experience of high flow bypass surgery for giant, fusiform and dissecting aneurysms, including combined surgical and radiological procedures which exclude the aneurysm from the circulation whilst maintaining distal flow.

Dr Joshi, an interventional neuroradiologist at Cambridge, described recent advances in neuro-interventional techniques including flow diverting stents WEB devices for example. He discussed the evidence base which remains strongest for simple coiling of ruptured aneurysms. He also described the interesting correlation that the rate of successful coiling increases in those units where a large number of aneurysms are clipped. This suggests that the expertise of the multidisciplinary team is key to a good outcome. The UKs first insertion of a steerable catheter into the radial artery to exclude an aneurysm was performed in Cambridge earlier this year and proved successful.

The panel discussion was followed by two patient perspectives, stroke survivor Mrs Printer, and AVM patient, Mrs Brown. These sessions offered a unique insight into life after a bleed in the brain.

Mrs Printer is a high profile judge who had to medically retire following an intracerebral bleed suffered whilst preparing for the London Marathon. She described the difficulties she had encountered getting the care she required, whilst maintaining her family and pursuing new directions in her professional and personal life. She explained the psychological and physical impact of specific disabilities such as hemianopia, and the artwork that she uses to give unique perspectives on this was available to view in lobby.

Mrs Brown gave an insightful talk on her life with an AVM. She has undertaken a Psychology degree to better understand the brain and also to be able to pursue a role in which she can draw from her own experience in order to help others. She gave an inspiring account of how dealing with her AVM has pushed her to take on new roles and challenges that she might not have done otherwise in her life before it was diagnosed.

The afternoon session started with some thought-provoking talks by the neuropsychologists, Dr Woodberry and Dr Browne, occupational therapist Ms Simpson and Lead Vascular CNS Ms Stoneley who highlighted how the key element for a good rehabilitation is making a daily plan with achievable goals. One of the most exciting tools they presented is a camera that the patient can carry with themselves to record their daily activities so that they can easily retrieve their memories. They explained the crucial role of focusing on patient's individual needs on the long road to recovery, and how to support patients through the ups and downs that characterise this journey.

The hot topic, AVMs, was presented by Mr Bulters, Consultant at the Wessex Neurological Centre. With a 2-4% annual risk of AVM rupture, the decision when and if to treat is carefully considered. The results of the ARUBA trial, in particular, are contentious, and Mr Bulters urged us to consider their conclusions with care due to selection and treatment bias. He concluded that due to the life-long nature of the disease, randomised controlled trials had proved to be impractical, and in the future registry data could be used instead to monitor and inform best practice.

Dr Gholkar, OBE reminded us that in his first days as a Consultant Neuro-radiologist in Newcastle, his senior colleagues taught him that stroke patients were not to be scanned. Clearly there has been a sea-change in management since then. He reviewed the array of non-invasive imaging techniques available today and discussed 3D angiograms which produce extremely accurate aneurysm reconstructions for planning complex coiling techniques.

The last presentation was a mix of basic sciences and clinical applications in the field of neuro-immunology by Mr Hiren Patel, Consultant Neurosurgeon at the Salford Royal. He undertook his PhD on neuroinflammation under the supervision of Professor Dame Rothwell, in an attempt to reduce brain injury in patients after aneurysmal subarachnoid haemorrhage. IL-1 induced inflammation of the brain is an important contributor to cerebral ischaemia. They have conducted a randomised, open-label, single-blinded study that supports the role of an interleukin-1 receptor antagonist (IL1-Ra) in an attempt to reduce peripheral inflammation after aneurysmal subarachnoid haemorrhage. These data support a Phase III study investigating the effect of IL-1Ra on outcome following aSAH.

To conclude, the presenters addressed the importance of a multidisciplinary approach to patient management, and innovation through collaboration to improve the lives of those with Neurovascular disorders. The day provided a unique perspective from a great variety of professionals and patients into the nature of such diseases, and optimism for their future management.

References

1. Evans M, White P, Cowley P and Werring, D. *Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy*. Practical Neurology, 2017;17(4):252-65

Encephalitis Conference 2017

Conference details: 4th December 2017, London, UK. ***Report by:*** John Wilson, University of Liverpool and edited by Dr Ava Easton, The Encephalitis Society.
Conflict of interest statement: None declared.

This was my first attendance at the Encephalitis Conference and I immediately knew that the 2017 event would be special when finding an empty seat was a greater challenge than navigating the London underground as a bona fide Northerner. On arrival, I was enthralled by the variety of disciplines and industries which were represented including neurologists, healthcare professionals, clinical psychologists and neuropsychologists, academics, researchers, and lawyers. The 2017 Encephalitis Society Professional`s Conference took place in front of a packed house at MacFarlane's LLP in central London, with delegates travelling from the US, the Netherlands, Denmark, UK, and Indonesia. Special thanks were in order for the Encephalitis Society who organised and sponsored the day along with other sponsors, which included MacFarlane`s LLP, Routledge publishers, the Auto-Immune Encephalitis Alliance, the University of Liverpool, and the Health Protection Research Unit for Emerging and Zoonotic Infections.

In his keynote address titled "A curiosity for cures", Professor Andrew Lees opened with his fantasia on the subject of Encephalitis Lethargica and of his unlikely mentor, William Burroughs, the author of many novels, short stories and essays, perhaps best known for his novel *Naked Lunch* and the infamous character, Doc Benway. Professor Lees reflected on the anti-bureaucratic stance of his mentor and the Faustian bargain which was later struck, ensuring Professor Lees completed his medical school training. The audience was then enlightened with a historical perspective of Encephalitis Lethargica in England, dating back 100 years to 1918, where it was mysteriously referred to as the "sleepy sickness". During the first few decades, the source of this mysterious illness was unknown, although doctors were powerless to assist patients, progress was made on ruling out early candidates of its onset, such as Spanish Flu or a cerebral variant of Polio. Within 20 years a hospital, Highlands Hospital in Enfield, North London was opened to care for the most severely affected patients of the early epidemic. This very hospital would later become the backdrop of the 1990 film "Awakenings", staring Robert De Niro and Robin Williams, drawing upon the personal accounts and experiences of Professor Lees and his patients.

Dr Marienke de Bruijn, of Erasmus University Medical Centre, Rotterdam, presented her work on long-term neuropsychological and behavioural outcomes in paediatric anti-NMDAR encephalitis. Dr de Bruijn reported differing clinical presentations within adult and paediatric anti-NMDAR encephalitis: children and adults present both with behavioural

keynote speaker Professor Andrew Lees

difficulties, additionally adults more with memory difficulties and children with epilepsy or movement disorders. Dr de Bruijn reported good outcomes for more than three quarters of the children in her study, although a sobering reflection was that only 60% of the children returned to school at their previous level, and persistent neuropsychological difficulties were reported.

Following Dr de Bruijn was Dr Jessie Cooper of the School of Health Sciences, University of London, with her presentation "Care beyond the hospital ward: understanding the socio-medical trajectory of HSVE". Dr Cooper highlighted how the rising number of survivors of Herpes Simplex Virus Encephalitis (HSVE) has led to an increasing number of people facing life with an acquired brain injury. Conducting interviews with participants affected by HSVE, several common themes emerged including how the daily lives of loved ones can be affected following HSVE, how a lack of access to support and structured rehabilitation for neuropsychological changes can make problems worse and how financial changes can affect the survivor and their family. Concluding her presentation, Dr Cooper identified several things that might ameliorate some of these difficulties, including the importance of giving the person and their family information about encephalitis and its sequelae after discharge from hospital and sign-posting to relevant places of support, such as the Encephalitis Society.

Dr Ronan McGinty from the Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Sciences, University of Oxford, presented research on autoantibodies in 232 adults with newly diagnosed focal epilepsy, 10 of whom had autoimmune encephalitis. Of these 10 patients, autoantibodies were detected in 7 (including antibodies to LGI1, CASPR2, GABA-a and GABA-b receptors, and the NMDA receptor), most had difficult-to-treat temporal lobe-onset seizures with inflammatory changes on MRI brain, and 4/6 treated with immunotherapy demonstrated an improvement in functional status. This study suggests that features of encephalitis could be useful clinical indicators of neuronal surface antibodies in adults with new focal-onset epilepsy and prompt early consideration of immunotherapy.

Dr Hannah Brindle of the Institute of Infection and Global Health, University of Liverpool, joined the conference remotely to present her work on Acute Encephalitis Syndrome (AES) from 1992-2015, in Vietnam. Dr Brindle informed the audience of the epidemiology of AES in Vietnam using surveillance data, with Japanese Encephalitis being the largest cause of AES in children; HSVE, dengue and enterovirus as the largest causes in adults; and roughly 50% of AES cases in Vietnam are of an unknown aetiology. Dr Brindle concluded her presentation reporting that peaks in the number of cases reported in northern Vietnam during the summer months are evidenced by a significant positive correlation between latitude and incidence of AES and interestingly that AES incidence is significantly correlated with irrigated land, supporting hypotheses that many cases of AES may be vector-borne.

Dr Julianne Brown, Clinical Scientist and Virologist at Great Ormond Street Hospital for Children, then presented "Should deep sequencing be routinely used for diagnosis of encephalitis?". Dr Brown highlighted the pros (relative speed and sensitivity) and cons (insufficient CSF specimen for multiple tests

of multiple targets) of the routine diagnostic method of encephalitis, polymerase chain reaction (PCR), contrasting this with another method, known as "deep sequencing" (DS) which uses RNAseq to identify the causes of encephalitis. Dr Brown`s recent work investigating the use of DS as an emerging application in identifying encephalitis has led to Dr Brown and her team being awarded a grant from Great Ormond Street Hospital Children's Charity, in order to set up a new diagnostic service for encephalitis.

After a light lunch kindly sponsored by the Autoimmune Encephalitis Alliance, Dr. Anusha Yeshokumar of the Icahn School of Medicine at Mount Sinai, NYC, outlined her study investigating long-term neurobehavioural impairment in patients with autoimmune encephalitis (AE). Several important conclusions were drawn from her study. While many AE patients may continue to experience poor outcomes following hospital discharge, patients with anti-NMDAR encephalitis may have better outcomes in neurologic disability and adaptive function than people affected by other forms of autoimmune encephalitis. Also, the persistent deficits experienced by patients may not be adequately captured by routine neurologic assessments alone.

Next, Maarten Titulaer, Assistant Professor at Erasmus University Medical Centre, The Netherlands, gave an elucidating keynote address titled, "Anti-GABAbr encephalitis: status epilepticus and beyond". Dr Titulaer highlighted that over 90% of patients in his study showed behaviour and cognitive changes and a similar percentage having seizures; of which 100% were tonic-clonic seizures, with over 40% of patients developing refractory status epilepticus (necessitating ICU admission). Several important take home messages from Dr Titulaer`s keynote address were that Anti-GABAbr encephalitis may present as a rapidly progressing dementia, that MRI of the brain can be normal and that limbic encephalitis can often present with refractory seizures.

Following the keynote address, Dr James Varley of the Oxford autoimmune neurology group presented his work on contactin associated protein-2 antibody mediated neurological conditions. Dr Varley highlighted several CASPR-2 antibody associated features, the three most common of which were, cognitive symptoms, psychiatric symptoms and seizures, with cognitive changes and neuropathic pain being reported as the most troublesome during recovery. Concluding his presentation, Dr Varley highlighted a clinical pattern across cohorts in CASPR-2 mediated neurological diseases and that despite generally good recovery rates, some persistent sequelae are the norm, rather than the exception.

Dr Sophie Binks, an academic clinical fellow at the Nuffield Department of Clinical Neurosciences, Oxford, rounded off the speaker presentations for the day with her work on long-term cognitive, psychiatric and quality of life sequelae in autoimmune and infectious encephalitides. Investigating LGI1 antibody autoimmune encephalitis and infective causes of encephalitis, Dr Binks underlined some early findings from her study which corroborate with other speakers from today; changes in cognition, behaviour and mood following encephalitis can affect the person as well as the families and carers of the patient, and also that these effects can be long-lasting following discharge from hospital.

After a short break and book signings of Life after Encephalitis by Encephalitis Society CEO, Dr Ava Easton and Roald Dahl`s Marvellous Medicine by Professor Tom Solomon, a wonderful day of informative keynote addresses and presentations from leading researchers across many institutions and several countries, concluded with Phillipa Chapman of the Encephalitis Society, who presented the Society`s work this year in a video titled "Year in Review". This really accentuated the amazing work done by the Society`s ambassadors, the families and survivors of those affected by encephalitis, and the Society itself. Recognising the role of the many representatives of the Society, Professor Barbara Wilson OBE, was presented with an award for 10 years of service as the Society's president, with a handsome limited edition book by her favourite artist, Bob Dylan. A Lifetime Achievement Award was presented to Professor Angela Vincent for her work that has resulted in improved outcomes for patients and decreased mortality and disability following encephalitis. Humbly accepting her award Professor Vincent stated how "very lucky (she) has been to have been in a such a great team for so long".

Conference awards were then bestowed on two worthy winners, for best poster and best speaker, from all the erudite work presented on the day. Dr Adam al Diwani was awarded the prize for best poster and Dr Julianne Brown for best oral presentation. Finally, Dr Tehmina Bharucha received the 2017 Johnny Sutton Travel Bursary.

In the final scheduled event for the day, Michael Milligan, a playwright and actor from the USA who has performed on Broadway and at the Edinburgh Fringe Festival, performed the UK premiere of his one-man play, "Side Effects". This play had the packed house gripped throughout and enacts a burned-out, disenchanted and increasingly distrustful Doctor, navigating the layers of bureaucracy which obfuscate his passion for providing the level of care which his father delivered, and which he otherwise wishes that he could offer.

The Encephalitis Conference 2017 concluded with a cheese and wine reception which provided an additional and welcome time for the speakers and presenters of the day to discuss their projects, research and potential future collaborations together, in a wonderfully engaging, supportive and scientific milieu.

If you are interested in attending the next conference, please become a professional member of the Society (membership is free) and you will receive registration details for the next Encephalitis Conference scheduled for Monday 3rd December 2018 in London. https://www.encephalitis.info/professional-membership

"Michael Milligan, a playwright and actor from the USA who has performed on Broadway and at the Edinburgh Fringe Festival, performed the UK premiere of his one-man play, "Side Effects"

From Holmes to House – 500 years of the diagnostic neurologist

Conference details: 20 March 2018, Royal College of Physicians, London, UK. ***Report by:*** Michael Zandi, National Hospital for Neurology and Neurosurgery. ***Conflict of interest statement:*** None declared. ***Published online:*** 3/04/18.

The Royal College of Physicians building, next to Regent's Park, was designed by Denys Lasdun, opened in 1964 as the 5th home of the RCP since foundation in 1518, and represented a leap forward from previous buildings. The site marks an intersection of an almost straight line between Sherlock Holmes' 221B Baker street address, and William R Gowers' birthplace in Mare Street, Hackney. One of many events to mark 500 years of the RCP, David Nicholl (Birmingham) organised this event which took place on the 20th March 2018 (what would be Gowers' 173rd birthday) jointly with the Association of British Neurologists. Speakers were asked to reflect on neurology past, present and future, with an eye on what would have been in the times of Sherlock Holmes and what could be in a near-future time of physician Dr Gregory House M.D. (portrayed by Hugh Laurie in the US television series created by David Shore). I enjoyed this meeting in its entirety which took a broad historical eye at progress in neurology, with discussion of the art of clinical information gathering, examination and reasoning, and also the impact of three major areas: neuroimmunology, neurogenetics and brain imaging. The meeting opened with two plenary lectures by Andrew Lees and Angela Vincent.

Eliminate the impossible, and whatever remains must be the truth" (Arthur Conan Doyle, The Sign of Four, 1890).

Andrew Lees (UCL) opened the meeting with William Gowers' legacy in clinical method, and drew comparisons with Arthur Conan Doyle's Sherlock Holmes. Advised to read The Complete Works of Sherlock Holmes by William Gooddy, Lees realised later that this was his introduction to the method of William Gowers. Edinburgh-born Conan Doyle was inspired by Joseph Bell, completed his MD in tabes dorsalis, and was likely to have attended some of Gowers' lectures in London. Beyond his 1886 Manual of Diseases of the Nervous System, many lectures from Gowers are available still via the British Medical Journal on-line, transcribed by his students in shorthand. Lees reminded us how Gowers and Conan Doyle both teach us to develop our skills of observation (become an expert on cigarette ash, sleeves, ears, the art of seeing what others cannot see), put prejudices aside, and hone abductive reasoning (reasoning backwards from the end point of a crime scene, or clinical scenario). Only through practising this method can neurologists learn to recognise diagnoses hidden in plain sight, and not fall in error through use of pattern recognition or algorithmic thinking. Perhaps 10 or 20 thousand hours of training on the wards and in the clinics seeing patients are needed to develop this skill and to spot 'black swans'.

Angela Vincent (Oxford) provided a historical tour of neuroimmunology, and in particular the story of myasthenia gravis from Thomas Willis's description in De Anime Brotorum (1672) to contributions by Simpson, Chang and Lee, and working with her own mentor Ricardo Miledi (1927-2017) when her own academic life and contributions began. This talk covered publishing scoops in the 1970s, a long working partnership with colleague John Newsom Davies (1932-2007), innovations with plasma exchange, genetic and autoimmune seronegative myasthenia gravis, to recent insights from IgG1 and IgG4 antibody subtypes across a range of diseases. Highlighting the immunological contributions of Paul Ehrlich (Nobel prize 1908 shared with Mechnikov), including prediction of magic bullet therapies and studies of maternal autoantibody transfer (though Ehrlich had discounted the possibility of autoimmunity), Vincent discussed her own work on arthrogryposis with Leslie Jacobson, and maternal transfer of caspr2 autoantibodies with Ester Coutinho most recently. Vincent then described her approach to antibody mediated central nervous system diseases, where one neuroimmunology methodology which has stood the test of time has been application of the Witebsky modified-Koch's postulates (latest iteration: Rose and Bona 1993). Finally Vincent speculated on a near-future in which House M.D. in the emergency room would use point-of-care rapid antibody assays allowing immediate prescription of plasma cell bespoke therapies.

In the remaining morning talks, Anu Jacob (Liverpool) spoke of the past, present and future of paraneoplastic disorders, from Trousseau's migratory thrombophlebitis through to Denny Brown's contributions in the 1940s and novel insights from genetics and immunotherapy-induced encephalitis. Current approaches in recognising paraneoplastic neurological disorders remain guided by advances in antibody assays and imaging including PET. Jacob discussed novel insights for pathogenesis and therapies from advanced-immunotherapy induced encephalitis. Belinda Lennox (Oxford) discussed whether schizophrenia could be considered a neurological disorder, described the ongoing fragmentation of care for patients with neuropsychiatric symptoms, and the problems of how psychiatrists and neurologists name similar phenomena differently. Quoting Tom Insel, in 2010 then head of the US National Institutes of Mental Health, "a century ago we had large public institutions for serious mental illness, tuberculosis and leprosy. Of these three, today only mental illness, especially schizophrenia, remains unchanged in prevalence and disability." Lennox highlighted the work of Eve Johnstone (Glasgow) in CT scanning in schizophrenia (1976) and described her own work exploring the role of immunity in psychosis. Nick Wood (UCL) had the task to describe advances in genetics from Mendel to Venter. Wood spoke of the lack of opportunity compared to cancer in brain diseases until recently, to the marked emergence of data and advances in knowledge in the last 5 years, in which changing thinking from "diseases to pathways" had been most effective. Wood discussed new techniques to find the "genes beneath the peaks" in Manhattan plots, and the need to solve genetic problems first to allow us to build the right models of diseases, including examples from LRRK2, and GCH1

rare coding variants in Parkinson's Disease. A highlight of this talk was a clear description of Mendelian Randomisation, and its power to act as an inexpensive surrogate for expensive pharmaceutical randomised trials, and reveal nature's own randomised controlled trials, with examples including a causal link between raised BMI and reduced risk of Parkinson's disease. Finally, highlighting one of the most impressive recent papers in neurogenetics and therapy (nusinersen for spinal muscular atrophy), reminding us all that a clear result is plain to see when found. After lunch, Doug Turnbull reminded the audience just how recent the 66 year history of mitochondrial genetics is, with a survey of work by Mitchell and Mitchell, Sanger, and the landmark of Anita Harding's work with John Morgan Hughes and Ian Holt. Turnbull discussed the serendipity of being able to measure respiratory chain function sensitively, how NHS specialised services have enabled driving forward rare disease research, and the ethics, advances, and changes in law in mitochondrial donation.

Back to Conan Doyle's Edinburgh for 3 of the last 4 speakers, Joanna Wardlaw (Edinburgh) then spoke of 123 years of imaging, a tale of accidental discoveries, rapid dissemination e.g. of the 1895 röntgenogram, ongoing issues around minimising exposure to radiation, and advances in brain vascular imaging. Paul Matthews (Imperial and UK Biobank) gave an update on the UK biobank imaging study (nearly up to a quarter of its target of 100K people in the UK scanned, imaging.ukbiobank.ac.uk). Rustam Al-Shahi Salman (Edinburgh) expanded a theme of preventing over-diagnosis and talked of the ongoing need to minimise the discovery of incidentalomas through practising defensive medicine by imaging, giving examples of where this '1 in 37 brain roulette' has resulted in harm. He gave a notable example of arteriovenous malformation bleeding risk data and subsequent coiling in which the evidence (ARUBA) suggests more harm is done by intervention than medical management alone, and a familiar account of how such data can be met with hostility in the medical community at first. Finally, Andrew Elder (Edinburgh, and medical director of MRCP(UK)) talked with urgency that the 'physical examination is in trouble', citing examples from the US where physical examination has not been part of postgraduate medical or surgical training since 1972, and tied up the last theme of the day with evidence that physical examination beats unfocused 'screening' investigation hands down, and of its therapeutic and teaching value.

Several speakers gave clinical and research examples to support Gowers' "It is always pleasant to be right, but it is generally a much more useful thing to be wrong" (Gowers, 1894). I found, as I walked back from this enjoyable day to the Bloomsbury present, the aphorisms and stories of revealed black swans most instructive, the advances in genetics the most full of promise, and the secure knowledge that the next scientific advances and next 500 years are (probably) unpredictable.

References

1. https://history.rcplondon.ac.uk/, https://www.rcplondon.ac.uk/events/holmes-house-500-years-diagnostic-neurologist
2. Scott A, Eadie MJ, Lees A. 2012. *William Richard Gowers 1845-1915: exploring the Victorian brain: a biography*, Vol., Oxford University Press, Oxford.
3. Lees, AJ. *The strange case of Dr William Gowers and Mr Sherlock Holmes*. Brain, 2015;138(7):2103-8 https://doi.org/10.1093/brain/awv144
4. Gowers WR. *A post-graduate lecture on mistaken diagnosis: delivered in the National Hospital for the Paralysed and Epileptic*. Br Med J 1894;2:1-3
5. vimeo.com/acnrjournal/lees (video interview with Andrew Lees, April 2017, with a section on Gowers at the Queen Square Library, video produced by Ben Crowe @erafilms)
6. Vincent A, et al. *Serological and experimental studies in different forms of myasthenia gravis*. Ann N Y Acad Sci. 2018 Feb;1413(1):143-153. doi: 10.1111/nyas.13592.
7. Rose NR, Bona C. *Defining criteria for autoimmune diseases (Witebsky's postulates revisited)* Immunol Today. 1993;14(9):426-30.
8. Noyce et al. *Estimating the causal influence of body mass index on risk of Parkinson disease: A Mendelian randomisation study*. PLoS Med. 2017;14(6):e1002314. doi: 10.1371/journal.pmed.1002314.
9. Holt IJ, Harding AE, Morgan-Hughes JA. *Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies*. Nature. 1988;331(6158):717-9.
10. Herbert M, Turnbull D. *Mitochondrial Donation - Clearing the Final Regulatory Hurdle in the United Kingdom*. N Engl J Med. 2017;376(2):171-3. doi: 10.1056/NEJMcibr1615669. Epub 2016 Dec 28.
11. Ballerini L, et al. *Perivascular Spaces Segmentation in Brain MRI Using Optimal 3D Filtering*. Sci Rep. 2018;8(1):2132. doi: 10.1038/s41598-018-19781-5.
12. Mohr JP et al. Lancet. *Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial*. 2014;383(9917):614-21. doi: 10.1016/S0140-6736(13)62302-8.
13. Elder A et al. *The Road Back to the Bedside*. JAMA. 2013;310(8):799-800. doi:10.1001/jama.2013.227195.

To list your event in this diary email Rachael@acnr.co.uk by 16 July, 2018

JUNE

European Neuro Convention
6-7 June, 2018; London, UK
FREE tickets at
www.neuroconvention.com

Parkinson's Advanced MasterClass – Parkinson's Academy
12-14 June, 2018; Halifax Hall, Sheffield
http://parkinsonsacademy.co/courses/advanced-masterclass-course/

The Rubik's Cube of Childhood Brain Injury – The Children's Trust National Paediatric Brain Injury Conference
Wednesday 20 June, 2018; The Royal Society of Medicine, London, UK
www.thechildrenstrust.org.uk/conference

The Royal Marsden Neuro-Oncology Conference: Managing Brain Metastases in the 21st Century
21 June, 2018; London, UK
More details and online booking:
www.royalmarsden.nhs.uk/conferences

MS Non-specialist MasterClass – MS Academy
26-28 June, 2018; Halifax Hall, Sheffield, UK
http://multiplesclerosisacademy.org/courses/general-ms-masterclass/

Rett Syndrome information event
29 June 2018 – 1.30pm to 4.00pm and
30 June 2018 – 9.30 to 4.30pm; Rhyl, Denbighshire, UK
Info from julie.benson@rettuk.org
http://www.rettuk.org/

JULY

British Society of Neuro-Oncology Annual Meeting
4-6 July, 2018; Winchester, UK
https://www.bnos.org.uk/events/bnos-conference/

Frontiers in Traumatic Brain Injury
5-6 July, 2018; London, UK
https://frontiersintbi.com

Short Course: The Comorbidities of Epilepsy
Friday, 6th July 2018, St George's University Hospital, Tooting, London, UK
https://www.sgul.ac.uk/study/professional/short-courses

ESNA (Epilepsy Nurses Association) Conference
Sunday 8 July & Monday 9 July 2018, Bristol, UK.
http://www.esna-online.org.uk/2-day-conference-2018-bristol
or E. ESNAepilepsynursesassociation@outlook.com

Challenges in Brain Injury Rehabilitation
11 July, 2018; Raphael Hospital, Kent, UK
http://www.raphaelhospital.co.uk/professionals/training-education/training-application.html

International Syringomyelia and Chiari Conference
17-20 July, 2018; Birmingham, UK
https://bit.ly/2H1yz7w
E. Samantha.Womack@aesculap-academy.com

SEPTEMBER

Parkinson's Foundation MasterClass – Parkinson's Academy
4-5 September, 2018; Halifax Hall, Sheffield, UK
http://parkinsonsacademy.co/courses/foundation-masterclass-course/

Royal College of Psychiatrists Faculty of Neuropsychiatry Annual Conference 2018
Thursday 13-Friday 14 September 2018, London, UK http://www.rcpsych.ac.uk/traininpsychiatry/conferencestraining/conferences/neuropsychiatryconference2018.aspx

ILAE British Chapter Annual Scientific Meeting
26-28 September, 2018; Birmingham, UK
Early Bird Rate available until the 30th July 2018
http://www.ilaebritishconference.org.uk/

OCTOBER

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
https://multiplesclerosisacademy.org/events/palliative-care-masterclass-sheffield/
T. 01143 27 02 30

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

NOVEMBER

MS Specialist MasterClass – MS Academy
21-23 November, 2018; Halifax Hall, Sheffield, UK
http://multiplesclerosisacademy.org/courses/specialist-ms-masterclass/

West of England Seminars in Advanced Neurology (WESAN)
22-23 November, 2018; Exeter, UK
http://www.wesan.org.uk/

DECEMBER

Encephalitis Conference
3 December, 2018; London, UK
https://www.encephalitis.info/Event/encephalitis-conference2018
T. 01653 692583, E. Alina@Encephalitis.info

UK Stroke Forum Conference
4-6 December; 2018; Telford, UK
https://www.stroke.org.uk/professionals

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
http://www.mindmoodmicrobes.org/index.php

FEBRUARY

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

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

EAN/WSO/AAN/IBRO/WFN/EHF/LINF 9th Regional Teaching Course (RTC) on Neurology

Conference details: November 8-11, 2017, Ougadougou, Burkina Faso, Sub-Saharan Africa. ***Report by:*** Peter Sandercock, Emeritus Professor of Neurology, University of Edinburgh, UK, Erich Schmutzhard (Chair of EAN task force), Professor of Neurology and Critical Care Medicine, Innsbruck, Austria and Eveline Sipido, European Academy of Neurology. ***Conflict of interest statement:*** None declared.

The 9th Regional Teaching Course (RTC) took place in Ouagadougou Burkina Faso on November 8 – 11, 2017. The meeting was hosted by Prof. Jean Kabore, Head of the Neurological Department of the Yalgado Ouedrago Hospital of Ouagadougou together with Prof. Athanase Milogo, Head of the Neurology Department of the Sanou Sourou hospital in Bo Bo Dialasso and Prof. Christian Napon, head of the Neurology Department of the District Hospital of Bogodogo, Ouagadougou. The RTC took place at the National Hospital "Blaise Compaore".

The RTC, organised by the EAN, was supported by a consortium of European and international scientific societies:

- University of Ougadougou, Burkina Faso
- WSO - World Stroke Organisation
- AFAN –African Academy of Neurology
- WFN - World Federation of Neurology
- AAN - American Academy of Neurology
- IBRO - International Brain Research Organisation
- International PD and Movement Disorder Society

Thanks to the funding received from the sponsoring scientific societies, 27 residents from 19 Sub-Saharan countries could be invited to the RTC. These residents have their flight and hotel paid for through this sponsorship. These individuals were selected by the course organisers from a larger number of neurological trainees who had been put forward by their Head of Department as potential course participants; these selected participants represent some of the very best trainees from across Africa. Additional trainees from the local area attended, bring the total attendance to 75 people.

The course was opened by Prof Jean Kabore, Prof Rabiou Cissé, Dean of the University of Ougadougou, Prof Claudine Lougué, Director of the Faculty of Medical Sciences of the University of Ougadougou and Prof Erich Schmutzhard, Director of the RTC. Prof Cissé welcomed all to Burkina Faso and was pleased that international neurology has come to "the land of the righteous men". He stressed the importance of the RTC and the opportunity given to the students to receive teaching of excellence from such a wide group of worldwide faculty. Prof Schmutzhard spoke about EAN, the "home for neurology". The pointed out that this home goes way beyond Europe. It is one of EAN's main goals to share knowledge of excellence through its educational activities. He pointed out that in Europe and in SSA, one out of three diseases are neurology related. It therefore is one of EAN's main goal to get neurology on the worldwide map of medicine. Prof. Rabiou Cissé, at the end of the speeches, declared the RTC open.

RTC Faculty and the Course participants

Opening ceremony (L to R): Prof Jean Kaboure, Professor Rabiou Cissé and Professor Erich Schmutzhard

The 2017 RTC addressed four topics of major interest for Sub-Saharan Africa:

- Stroke
- Movement Disorders and Dementia
- Neuromuscular diseases
- Spinal Cord diseases

Faculty from Africa, Europe and America attended the RTC. The core organisation of the course is led by the "Neurology and SSA" Task Force team at the European Academy of Neurology (EAN). The high international reputation for academic excellence of the course is underlined by the wide range of learned societies and institutions that support this annual course. The Faculty for the Stroke section was Amadou Gallo Diop (Senegal), Jose Ferro (Portugal), Peter Sandercock (UK), Yomi Ogun (Nigeria), for Movement Disorders and Dementia was Njideka Okubadejo (Nigeria), David Riley (USA), Raj Kalaria (UK), for Spinal Cord Disorders was Augustine Charway Felli, (Ghana), Riadh Gouider (Tunisia), Osheik Seidi (Sudan) and for Neuromuscular Disorders was Jean Kaboure (Burkina Faso), Wolfgang Grisold (Austria) Jean Michel Vallat (France).

The topic for day one was Stroke in Sub-Saharan Africa. Prof Amadou Gallo Diop (WFN) gave an overview of the epidemiology and classification of Stroke in Sub-Saharan Africa. He was followed by Peter Sandercock (WSO) who lectured on the clinical presentations, signs and symptoms of stroke. Prof Jose Ferro (EAN) illustrated the state of the art in diagnostic work-up and therapeutic management of stroke while Prof Yomi Ogun (AFAN) spoke of the state of the art and specifics of stroke diagnostics and therapeutic management of stroke in urban and rural SSA. Prof Erich Schmutzhard (EAN) and Prof Raj Kalaria (IBRO) moderated the Clinical Grand Round in which we discussed a case, selected by the faculty from among the many received, of possible vasculitis which was presented by Bademain Jean Fabrice Ido from Burkina Faso. The afternoon small group interactive workshops led by the Faculty discussed cases brought by the course participants and faculty. Interesting intercultural discussion followed presentation of cases with severe stroke, contrasting the different approaches to

breaking bad news taken in Europe and Africa. The case discussions were, and the preference of many families followed in the evening by a welcome reception, offered by the local organising committee.

The topic for day 2 was Movement Disorders and Dementia in Sub-Saharan Africa. Njideka Okubadejo gave a comprehensive overview of the epidemiology and classification of movement disorders, David Riley covered the diagnosis diagnostic work-up and management of movement disorders. Raj Kalaria (UK) gave an overview of the dementias in SSA. For the Grand Round Case presentations, the moderators were Amadou Gallo Diop and and the discussants were David Riley, Raj Kalaria and Njideka Okubadejo. The speakers emphasised the importance of clinical assessment and observation in the diagnosis and the limited value of costly imaging studies in diagnosis. The cases were of a case of segmental dystonia presented by Emanuel Epunge Djonga from Democratic Republic of Congo and of Dementia in young woman by Mahamadi Oudraougo from Burkina Faso. The afternoon was again given over to case discussion workshops.

The topic for day 3 was Spinal Cord Disorders in Sub-Saharan Africa. Augustine Charway Felli reviewed the epidemiology and classification, Riadh Gouider discussed the clinical presentation, symptoms and signs of spinal cord disorders and Osheik Seidi set out the diagnostic work-up and management from an African perspective. The speakers highlighted the lack of community-based epidemiological studies, the frequency of traumatic spinal cord injury and tuberculous spinal disease and the need for long-term management of patients with spinal cord damage. For the Grand Round Case presentations, the moderators were Wolfgang Grisold and Yomi Ogun, the discussants were Augustine Charway Felli and Riadh Gouider. Dr Razafindrazata from Madagascar presented a case of tuberculosis complicated by an intramedullary tuberculoma at T6 and Potts disease at L1-2. Dr Patrick Feussouo from Burkina Faso presented a case of a case of multiple sclerosis. The afternoon was again given over to case discussion workshops. The course dinner was a lively affair; a highlight was the series of short speeches on their country's characteristics and special attributes from a representative of each country attending the course.

The topic for day 4 was Neuromuscular Disorders in Sub-Saharan Africa. Jean Kaboure gave an overview of the epidemiology and classification, Wolfgang Grisold spoke on the clinical presentations and Jean Michel Vallat on the therapeutic management with EMG examples. For the Grand Round Case presentations, the moderators were Osheik Seidi and Erich Schmutzhard, the discussants were Jean Kabore, Wolfgang Grisold and Jean-Michel Vallat. Dr Hiba Hassan Abugabal (Sudan) presented a case of hypokalaemic periodic paralysis and Dr Yusuf Jamnagerwalla presented a case of juvenile dermato-mysositis. The afternoon was again given over to case discussion workshops.

The Grand Round discussions each day provided a forum to discuss how clinical reasoning should progress in a linear fashion from clinical history, physical examination, clinical localisation of the neurological lesion, basic investigation and finally advanced imaging if available. The trainees brought a great many questions that arose from their daily practice; this unique opportunity for them to ask the Faculty questions and to network with their peers from across the continent was something they really valued. At the end of each day, participants completed a short multiple choice exam on the topic of the day. The accumulated results revealed that the learning objectives had been achieved to a high level. Participants also completed an on-line feedback questionnaire.

The meeting was organised to a very high standard, and clearly meets the need to build capacity in caring for people with neurological disorders in the African continent, where the burden of disease related to both communicable and non-communicable diseases of the nervous system is high. To meet this continuing need, the EAN-led planning group met in Ougadougou to plan the next course. The participants to the 9th RTC were asked to list up to three topics of interest they would like to see addressed in a future RTC. From the compilation of the topics received, three that had the highest request were identified for the 2018 RTC. This 10th RTC will be held in Madagascar in October 2018.

PREVIEW: Royal College of Psychiatrists Faculty of Neuropsychiatry Conference

Conference details: 13-14 September 2018, RCPsych, London, UK. ***Report by:*** Dr George El-Nimr, Academic Secretary.

This year the faculty's annual conference will take place on 13 – 14 September 2018. The event will cover a range of issues pertinent to those working in the field of neuropsychiatry, building on the success of previous annual conferences, which have enjoyed strong support from national and international colleagues.

Topics include recent advances in functional neurological disorders, epilepsy and neurodegenerative conditions, as well as a plenary session on neurosciences and their application to everyday practice. Delegates will have the opportunity to update their knowledge and skills on neuroimaging and neurophysiological tests and their practical use in delivering high quality clinical care to patients.

Relevant legal and ethical issues will also be discussed. 'New Conceptions of the Mind' will be presented to cover topics such as computational psychiatry and rational psychiatry.

As in previous years, medical humanities and their relevance to clinical practice will also have their place within the conference. Delegates will hear from eminent speakers about concepts such as 'Neurodogma', 'Neuromania' and 'Neuromythology'!

In addition to poster presentations, a Trainee Award presentations session will be dedicated for trainees to present their research and audit projects.

The conference is supported by a host of distinguished speakers utilising different educational styles and teaching formats. Similar to previous years, a selection of seminars will cover various clinical, service and medicolegal issues as well as update delegates on advanced research developments. These include sleep disorders, behavioural challenges in acquired brain injury, paediatric neuropsychiatry and the neuropsychiatric assessment of 'funny turns'.

As the conference tends to be oversubscribed, colleagues are advised to book their place to avoid disappointment!

A line-up of eminent speakers have already confirmed their attendance; these include:

- Professor Lisa Bortolotti
- Professor Andrea Cavana
- Professor Shoumi Deb
- Dr Chris Derry
- Professor Ray Dolan
- Professor Mark Edwards
- Professor Rafey Faruqui
- Professor Karl Friston
- Dr Paul Johns
- Professor Andrew Lees
- Dr Aileen McGonigal
- Dr Nandini Mullatti
- Dr Maria Oto
- Professor Ray Tallis

Society for Research in Rehabilitation

Conference details: 6 February, 2018; Bristol, UK. ***Report by:*** Derick Wade, Consultant in Neurological Rehabilitation, Oxford University Hospitals, UK.
Conflict of interest statement: None declared. ***Published online:*** 28/3/18

"The hospital should ask its doctors which meetings they want funding to attend. And then they should let the doctors know they can have the full amount of money requested. But . ?"

This is a personal account of new ideas and facts that I acquired in five hours at an exciting and excellent meeting where I also met many friends and colleagues who added, greatly, both to enjoyment and to learning.

The most striking outcome for me was a realisation that, although I read all articles submitted to Clinical Rehabilitation, I search regularly in relation to a book on rehabilitation, and I have been interested in most aspects of rehabilitation for 37 years, nonetheless I learned about major and important ideas and developments that I had absolutely not heard about. How can this happen?

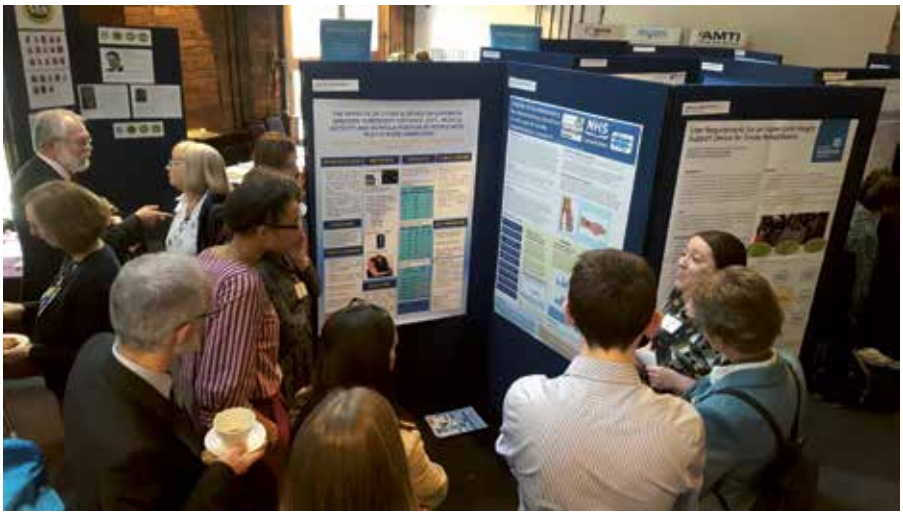
Generally I, like most people, go to meetings which focus on areas that I am particularly interested in, and may even be expert in. I obviously meet others with similar interests, many are also friends. We may learn a few small facts, but generally we all know what each of us is doing, and we all read much the same material. It is a very comfortable experience, reassuring me that what I know or think is correct, and maybe introducing a further new fact or idea entirely within an existing model or framework.

Further, employers have a narrow view on continuing professional development. They ignore the third and most important word, DEVELOPMENT. Instead they focus on increasing targeted knowledge and skills. Employers are then surprised, when trying to alter or improve services, that staff do not come up with any particularly new ideas. They then spend a fortune on external advisors who know nothing, except how to charge large sums to suggest either obvious or inappropriate and/or impossible ideas.

The reason this meeting was so full of new and different ideas for me, and I think it was for most people, was precisely because most of us were outside our comfort zone for most of the time. Of course there was an underlying general interest in rehabilitation but the range of different professions and the range of different healthcare and non-healthcare specialities represented was large. There was always someone to ask the awkward but insightful question, and someone else to give an alternative valid answer.

The next part of the initial quotation was: *"But you are not allowed to use any of it on any of the meetings you requested!"*

Though the quotation is not verbatim, it was the message given by David Sacket speaking at the Radcliffe Infirmary about 20 years ago. He emphasised the great importance of and benefits that arise from going to meeting well outside your own small area of interest.



Claire Mitchell collected her double Verna Wright prize as the winner of the Oral and Poster prizes in 2017.

Dr Emma Patchick, University of Manchester and NIHR CLAHRC GM won the Best Work in Progress Poster.

Content of five main presentations

A personal view

Nicola Walsh started her talk considering evidence for effective therapies for people with knee osteo-arthritis, which concluded that exercise and changing behaviour were both important. Most importantly, she then broadened her view to encompass (a) other similar disorders and (b) practical considerations, especially affordability. She concluded that the role of a rehabilitation team was to diagnose correctly (understand what was wrong, and what could be done), and then to refer to non-health, 'normal' community resources where exercise professionals with training in behavioural change strategies would help the person learn to exercise as part of normal life.

Candy McCabe illustrated the principle of (a) gaining a proper understanding and (b) using this to design an approach for the patient to use with (c) education of the patient; her chosen population was people with complex regional pain syndrome. She showed how normal pain mechanisms, essential to protect us from harm, can become distorted (why is unknown), becoming excessively vigilant and responsive to at least some aspects of the threat. This distorts perception of bodily parts and bodily function. A treatment approach based on this analysis, using virtual reality and many other techniques works; analgesia is spectacularly unsuccessful.

Garth Johnson spoke about bioengineering in rehabilitation. Completely unexpectedly (to me), he highlighted the role that bioengineers and a bioengineering approach have in analysing and understanding any disorder of movement, from joint arthritis to disordered motor control after stroke. The outcome of understanding joint function has been demonstrated in the development of increasingly complex, and successful joint replacement.

However the emphasis was on neurologically disordered motor control, and he showed how bioengineering data could answer questions that neurophysiological investigation could not.

Roshan dasNair took a different approach – his interest was in rehabilitation for cognitive deficits, specifically memory problems in people with multiple sclerosis. He started by disabusing us of the belief that systematic reviews were necessarily a sound evidence base, citing a widely quoted systematic review that concluded that there is good evidence that cognitive rehabilitation helps people with memory deficits. A critical review (by another group) showed that there was in fact no evidence to support the conclusion. He then told us about his (to be published soon) large trial, which had not found evidence of benefit across a range of outcomes.

Carolyn Young, the last speaker, also talked about multiple sclerosis. She started with a question – how many of us had heard of or knew about the TONiC study? Very few, if any. Yet it has recruited 25% of all patients with motor neurone disease (MND) in England, and over 7,000 people with multiple sclerosis (MS) from England. It is the 'Trajectories of Outcomes in Neurological Conditions (TONiC) study' and has permission to study not only MS and MND but also traumatic brain injury and neuro-muscular condition. She also told us about the Wilson and Cleary 'conceptual model of patient outcomes', based on the biopsychosocial model. Watch the TONiC study; it will potentially help rehabilitation greatly. https://tonic.thewaltoncentre.nhs.uk/

Cambridge Dementia Course 2017

Conference details: 6-8 December, 2017, Cambridge, UK. ***Report by:*** Julia Greenland, neurology registrar and clinical research associate at John van Geest Centre for Brain Repair, Cambridge. ***Conflict of interest statement:*** The author is a Cambridge trainee and her fees for the course were paid for.

I attended the Cambridge Dementia course in December 2017, in my first year as a neurology registrar. It had been recommended it by colleagues, and I found that it gave a practical and fascinating overview of this field. In my view, the balance between the clinical aspects and the underlying pathology and science was well conceived. There were talks from world-class speakers, all of whom were clearly passionate about their fields and gave insight into current research and potential future therapies.

The conference was held over three days at the Homerton College, Cambridge. It was a picturesque setting, from arriving and walking through the grounds to the college, to lunch in the great hall, complete with giant Christmas tree. But despite the chilly, grey December days, the conference venue itself was surprisingly cosy. Plus, we were we were plied with regular hot drinks and selections of biscuits and tasty pastries.

The course was attended by professionals from a range of backgrounds. From the beginning we were asked to identify with "team neurology" or "team psychiatry". My choice has already been made, but I was entertained that my friend, a geriatrician, chose to side with the psychiatrists. It was fun, of course, and equally there were clearly other disciplines represented, including GPs, psychologists and specialist nurses. But this was a theme that ran through the conference; there are different perspectives on each of the conditions that were discussed. It certainly encouraged a very holistic view.

The event started with an introduction from Dr Jeremy Brown and Dr Andrew Graham. Their enthusiasm for the subject and dedication to teaching was palpable from the onset and set the tone. Together they chaired the sessions over the three days. The introduction covered a structured clinical approach to a patient presenting with memory problems. Particularly useful were pointers on how to discriminate the patient with cognitive problems from the worried well. Would I ever make that mistake? (With the case of "Do you have to be told the same things many times?" just ask my husband).

For me, it was the videos that elevated the conference. Like most of my colleagues, I find that it is the individual patients and their stories that illustrate a learning point. We saw examples of a wide range of conditions, from typical Alzheimer's disease, with which we were all familiar, to semantic dementia and posterior cortical atrophy. The videos gave us a chance to sit back and concentrate on watching and listening.

Within a short space of time, we all felt like experts. We were spotting the "head-turn" sign with confidence (a patient with dementia turning to look at their spouse after being asked a question, apparently equating to approximately moderate dementia).

The videos also illustrated how to examine patients with cognitive impairment in a way that flowed seamlessly from the history. We learnt about the technique of "repeat and define", which has led me to practise saying the word "chrysanthemum". Present in all of these examinations were small plastic animals; which emerged from beneath the table as if this was an expected part of a consultation with any doctor. The use of these animals in the videos illustrated different language impairments more eloquently than could possibly be achieved solely through lectures.

The lectures thoroughly covered the range of conditions that might present to a memory clinic, including some rarities. From Professor John Hodges we heard about the frontotemporal dementias. We followed these conditions from the underlying pathology, the genetic component and the imaging findings to the clinical presentations and related conditions. There were more videos, consolidating our knowledge. The plastic animals made yet more appearances, and we watched a woman with semantic dementia who had seemed to navigate the consultation fluently struggle to define a caterpillar; "Not a cat".

Dr Amanda Cox talked about limbic encephalitis, giving an insight into the expanding array of antibodies and the management and prognosis of this treatable set of conditions. Another highlight was the talk on prion disease by Professor Simon Mead, who stressed the variability of its presentation and the clues for diagnosis on imaging and the RT-QUIC test.

Psychiatry was also represented. From a very practical guide on managing behavioural and psychological symptoms in dementia, to a talk by Dr Fiona Thompson about the importance of considering depression in patients with dementia, though illustrating how sometimes it can be difficult to differentiate the two clinically. Professor Rob Howard summed up a number of key points in a talk entitled "Psychiatry for neurologists".

PSP and CBD were presented by Professor James Rowe, and Huntington's disease by Professor Roger Barker. We learnt from both of their extensive clinical experience and gained new insight into symptomatic treatment, imaging techniques and current research in these conditions.

The lectures were broken up with smaller group workshops which were run by neuropsychologists. These gave us a first-hand and informative way to find out about the various cognitive tests and how they can discriminate between different domains of cognition. We tested our executive function with the Stroop test and tried to copy the Rey complex figure. Importantly, the neuropsychology score sheets that we had been given to interpret slowly became decipherable.

Furthermore, there was a specific focus on imaging on days two and three. As a new trainee, I found that Professor Nick Fox took a clear approach, starting from the basics. He thoroughly illustrated the diagnostic benefit of imaging in dementia, beyond ruling out other pathology.

The course was an intense three days. However, I enjoyed being immersed in the topic. The speakers were all approachable, questions were encouraged and there was a good amount of audience participation, culminating in an interactive quiz.

Currently my young son only has a set of plastic dinosaurs. I think it might be a little unfair to ask someone with cognitive problems to name an iguanodon. Or repeat micropachycephalosaurus. So instead, the dementia course has convinced me that I need to invest in a set of small model farm-yard animals. My son might be a little disappointed when they end up living in my work bag.

BNPA 2018 AGM Report

Conference details: March 1st-2nd, 2018, London, UK. ***Report by:*** Dr Thomas E Cope, BNPA committee neurology trainee representative.
Conflict of interest statement: None declared.

Despite the 'Beast from the East' freezing the transport infrastructure of our sceptred isle, two hundred and eighty three intrepid psychiatrists, neurologists, psychologists, rehabilitation medics, elderly care physicians and assorted others gathered in March for the 31st Annual General Meeting of the British Neuropsychiatry Association (BNPA).

The first session focused on sleep – start as you mean to go on, one might think, but three exciting and dynamic speakers ensured that there was no excessive daytime somnolence in the Kings Place auditorium. Russell Foster opened proceedings with a masterful and comprehensive overview of the neurobiological mechanisms of sleep. This set the scene beautifully for Kirstie Anderson, who gave a clinical perspective; providing a wonderfully dynamic and practical approach to the diagnosis and management of sleep disorders. While pharmacotherapy has a significant and appropriate role in sleep medicine, there is an increasing emphasis on cognitive and behavioural approaches, which can be curative. This is especially true of insomnia, and the session concluded with Eus van Someren giving a truly fascinating talk on the cognitive science of this highly prevalent and economically costly disorder, with an occasional segue into the cringing social embarrassment of bad karaoke.

After some light refreshment, the audience returned for a special session on shell shock, as we approach the centenary of the end of World War I. Simon Wessely kicked off with an historical review worthy of BBC4, covering the birth of a new epidemic disorder, the fumblings towards a therapeutic response (which differed starkly between the officers and enlisted men) and the eventual official prohibition of the diagnosis. Through the use of powerful archive video and dissection of clinical criteria, Prof Wessely effectively persuaded us all that, despite the prevailing cultural representations, shell shock shared little with modern ideas of post-traumatic stress disorder (PTSD) and was instead rather like what we would now term functional neurological disorders. To emphasise the contrast between the disorders, Chris Brewin then gave an up-to-the-moment talk on the past, present and future of PTSD. The audience were confronted with the clinical heterogeneity of this disorder, which is reflected in divergent diagnostic criteria, presenting a significant challenge to any proposal for one-size-fits-all management.

A hearty lunch was accompanied by further viewings of archive shell shock footage on big screens, providing a unique window into the birth of divergent therapeutic strategies for functional neurological disorders. After this, the highlight that is the BNPA poster session walkaround attracted great interest. We had a

Poster winners (L-R): Isobel A Williams, Reza Kiani and Nadja Bednarczuk.

wonderful array of thirty posters on display this year. The high quality resulted in a hard time for judges picking winners for the poster prize, but agreement was reached that the awards should go to Reza Kiani, Dept Health Sciences, University of Leicester "A study of autism and congenital blindness in adults with intellectual disability", Nadja Bednarczuk, Imperial College London, "Hemispheric Dominance: the link between Anxiety and the Vestibular System?", and Isobel A Williams, Dept of Psychology, University of Sheffield, "Reduced resting vagal tone in patients with Functional Neurological Disorder is associated with emotion dysregulation and psychopathology".

This year's JNNP guest speaker is the 26th most cited scientist of all time with 184,263 citations; h-index 202 – for reference Sigmund Freud is number 1 with 482,648 citations; h-index 272! An artificial intelligence known as Semantic Scholar named him as the most influential brain scientist of the modern era (sorry Sigmund). The central idea, set out with clarity and brilliance by Karl Friston, is that the brain acts as a predictive engine at every possible level. What we see and hear is not a representation of our sensory input, but rather an interpretation in the context of our previous experience, biases and beliefs. When these predictive mechanisms go wrong they can account for an extremely diverse range of conditions including schizophrenia, tinnitus, functional neurological disorder, and non-fluent aphasia.

After further refreshment, the winners of the Alwyn Lishman award gave the members' platform presentations. Lorenzo Caciagli presented the results of his neuropsychometry and fMRI study of cognitive dysfunction in frontal lobe epilepsy. João Miguel Fernandes then presented a novel non-verbal measure of social cognitive deficits in autism. Unfortunately, Sharon Savage was unable to make it through the snow, so Adam Zeman presented in her place on long-term follow-up of memory symptoms in transient epileptic amnesia.

Rounding off the talks for the day was the now-customary BNPA research update, in which we bring the audience up to speed with an of-the-moment topic. Nothing has attracted as much recent attention as new genetic therapies for Huntington's disease. David Craufurd clearly separated the hope from the hype and provided us all with a clear impression of the current state of treatment development. Non-invasive brain-state modulation with transcranial magnetic stimulation and transcranial direct current stimulation shows potential for translation from research tool to clinical practice in a number of domains. Camilla Nord conveyed the excitement and controversy of this emerging field with such dynamism and enthusiasm that she was almost immediately co-opted to the BNPA committee – we welcome her as the new junior representative for psychologists.

The BNPA evening reception in the postal museum had it all. Pizza, Royal Mail history, unlimited bar, cockney knees-up, chocolate brownies, new friends and good times. If you didn't make it this year, then etch the date in your diary for next year and practice your singing in the shower.

Day two commenced with a double-session on social cognition. Antonia Hamilton began by describing her beautiful studies of social cognition, in which children with autism performed better at goal-directed tasks by efficiently ignoring irrelevant experimenter actions that were copied by typically developing children. Boyd Ghosh gave an overview of under-recognised social cognition deficits in dementia, with special reference to how we should modify our information giving strategy to patients and relatives in frontotemporal lobar disorders including progressive supranuclear palsy. With Robin Dunbar stuck in Welsh snow drifts, Jeremy Schmahmann kindly stepped in with a double-length, comprehensive and clear description of the role of the cerebellum in emotion and cognition. So seminal has been his contribution to this field, that cerebellar cognitive affective syndrome is now known by many as Schmahmann's syndrome.

After lunch and posters, the BNPA medal was awarded to Michael Trimble, who gave a valedictory lecture on the brain basis of musical cognition and emotion, with special reference to the works of Elgar. As the culmination of the gathering, Iain McGilchrist delivered the special guest lecture on hemispheric specialisation in the brain. As thought provoking and inspiring as The Master and His Emissary, the audience were enraptured and, despite the implications of snow and ice for homewards travel, the lecture theatre remained full to the end.

The next BNPA AGM will be on 7th and 8th March 2019, again in Kings Place, which proved such a spectacular, practical and deliciously catered venue. We hope to see you all there, and at the BNPA teaching weekend 7th-9th December 2018.

Taking music therapy into the mainstream

Conference details: March 15th, 2018, London, UK. ***Report by:*** Daniel Thomas, Joint Managing Director at Chroma. ***Conflict of interest statement:*** None declared.

Every 90 seconds, someone in the UK is admitted to hospital with an Acquired Brain Injury.

With over one million people in the UK currently living with the effects of a brain injury the estimated bill to the UK is £15 billion. The devastating impact radiates across families causing distress, relationship strain, financial hardship and an uncertain future. The injury has a huge physical and psychological payload.

Neurologic Music Therapy (NMT) offers an effective rehabilitation treatment that is backed by a wealth of clinical evidence and has been shown to have a profound influence on the brain. However, raising awareness of the benefits of arts therapies, including NMT, can be extremely difficult.

Chroma's recent ABI conference entitled 'Arts Therapies and Brain Injury: Optimising Outcomes Across Assessment, Treatment and Care' brought together some of the leading international authorities and influencers in the arts therapies field. They delivered the latest research and scientific evidence on how arts therapies are improving outcomes for patients recovering from acquired brain injuries.

Chris Bryant, MP, and chair of the All Party Parliamentary Group on Acquired Brain Injury opened the conference by highlighting the growing problem of brain injuries and the wider impact it has on society.

Caroline Klage, Head of the Child Brain Injury Team at leading niche London law firm, Bolt Burdon Kemp, who sponsored the conference, welcomed the delegates.

She said: "As a firm, Bolt Burdon Kemp is keen to support NMT and raise awareness of its benefits. We are driven by the desire to ensure our clients receive the best quality input at the earliest point possible, with a view of enabling them to flourish and thrive post brain injury. NMT definitely has a role to play in that."

Dr Jeanette Tamplin, of the University of Melbourne, provided an introduction to the evolving field of the creative arts therapies, specifically Neurologic Music Therapy. Dr Tamplin is pioneering the use of Virtual Reality to improve the participation and engagement of rehab patients on music therapy protocols.

"Music can bypass damaged areas, providing a scaffold to do the part of the work the brain is not doing in coordinating movement. But there is also the basic 'use it or lose it principle'. When you exercise something, it gets stronger and the more you exercise, the better it becomes."

The inspiring responses seen in some cases still needs to be backed up by more clinical research and Dr Tamplin added: "I want people to understand that we are an evidence-based profession and there are functional outcomes from music therapy.

"There are amazing benefits for quality of life and participating in life as well as being able to walk a bit better. Music makes us feel better and we use it in ways to help us through life but I'd like people to understand the research and evidence behind what we are doing."

Sarah Johnson, a Neurologic Music Therapist and NMT pioneer from Colorado State University, presented a session on demonstrating the efficacy of NMT. She outlined the 'Transformational Design Model' a system that uses a clinical reasoning process to link assessments, goals, and learning through music.

Using case studies, video examples and clinical data, Sarah O'Doherty and Rebecca O'Connor, from the National Rehabilitation Hospital in Ireland, illustrated an innovative approach to assessing and treating children with acquired brain injuries. The approach involves a systematic observation and recording of the development of the child by a neuropsychologist during a music therapy treatment.

Practical hands-on workshops on applications in neuro-rehabilitation and articulating art therapy allowed delegates to experience, engage with and understand an arts therapy process from a client's/patient's point of view.

Dr Wendy Magee, a professor in the Music Therapy Department, at Temple University, Philadelphia, US showcased the MATADOC assessment for patients with prolonged disorders of consciousness (PDOC) that she and her colleagues pioneered.

According to Dr Magee, music is the auxiliary engine that has the power to reboot the brain following a catastrophic head injury, tumour or stroke. Dr Magee said: "A human being is born with the capacity to express emotions such as distress, anger and pleasure through musical parameters such as volume, dynamic range, pitch and melodic contour. So, in working with people who have lost the ability to communicate we can see that music is an innate way to communicate feelings.

"There is strong neurological evidence that music activates many different areas across the brain. The motor system is very sensitive to picking up cues from the auditory system so when we hear music, particularly pulse or rhythm, it kicks straight into the motor system going around the brain."

Summing up the conference, Daniel Thomas, managing director of Chroma, who organised the event, said: "As a neurologic music therapist and parent, I am deeply aware of the need for arts therapies to be provided in line with the rehabilitation code at the earliest possible point in someone's recovery.

"As a profession, we regularly punch above our weight and this conference has demonstrated our ability to make a significant difference to the lives of people with brain injuries, their families and the professional teams around them.

"It has also given a glimpse into the future developments of arts therapies and shown how it can be an absolutely essential rehabilitation treatment in mainstream health services."

National Neurosciences Advisory Group Neuromuscular event

Conference details: February 23rd, 2018, Queen Square, London, UK. ***Report by:*** Lucy Hawkins, Senior Consultant, The Strategy Unit at NHS Midlands and Lancashire Commissioning Support Unit. ***Conflict of interest statement:*** None declared.

An event focusing on Neuromuscular disease was held on the 23rd February 2018 as part of the National Neurosciences Advisory Group's wider scheme of work. The purpose of the day was to facilitate the improvement of services for patients with Neuromuscular disease nationally, through the sharing of good practice and identification of areas where more work is needed. It was acknowledged that different models of care will work in different parts of the country but equity in the standard of care is the goal.

The National Neurosciences Advisory Group (NNAG) exists to seek alignment between programmes in NHS England, the Department of Health's Arm's Length Bodies, and system partners, such as charities relevant to people with neurological conditions, and to guide the strategic development of work to improve outcomes for people living with neurological conditions. One of the aims of NNAG is to bring together all the different professionals that need to work together to achieve improvement in neurology services including clinicians, patients, commissioners and academics.

This event was the first of several events that will be taking place throughout the year. In March we looked at Neurorehabilitation, a meeting to look at Parkinson's, Dementia and Psychiatry is scheduled for July, followed by Epilepsy in September.

A number of presentations generated discussion around their potential for wider adoption or key issues that needed to be addressed.

The University College London Hospital (UCLH) Neuromuscular Complex Care Centre model, presented by Dr Ros Quinlivan, was highlighted as an area of good practice, this specially designed elective ward provides a one-stop-shop service for patients. This has been particularly valuable for a cohort who may fatigue easily and have trouble travelling to access services. The results have been holistic, streamlined, high quality care with improved communication between specialists and a 42% reduction in unplanned admissions for patients who have been assessed on the NMCCC more than once. It was agreed that work should be done to adapt this model for use in other regions, with initial discussions already taking place in Newcastle.

Lisa Joyce, Myasthenia Clinical Nurse Specialist (CNS) from University Hospital Southampton, presented on the work that she has been doing and the benefits delivered by her role. Lisa demonstrated that CNS posts deliver high quality service for patients, are highly valued by clinicians, and also delivered cost savings through the reduction of both Consultant appointments and unplanned hospital admissions. It was agreed that a business case should be developed to support the expansion of these roles nationally.

A key area of development presented by Dr Chiara Marini Bettolo was around emergent drugs for patients with Duchenne Muscular Dystrophy and Spinal Muscular Atrophy. She discussed increasing numbers of trials and novel treatments being developed for these conditions which is a positive step for patients with these conditions. However, she also highlighted a number of issues around equity of access to treatment, particularly through transition from paediatric to adult services, and that the appraisal process for these new treatments needs to be considered, particularly around longer-term resourcing implications.

Dr Yusuf Rajabally demonstrated how the process for IVIg prescribing is in need of improvement. He presented several case studies demonstrating issues of differences in access, discrepancies in approval, varying functions of approval panels, variable post usage queries and differences in long term monitoring. The result of this is patients receiving either inappropriate treatment, or unnecessary high doses of an expensive treatment. As a result of discussions, a new group has been established bringing together experts from the clinical reference groups to review the IVIg process.

Continuing the theme of access to treatment Dr David Hilton presented on access to Rituximab for Myasthenia Gravis. Rituximab is used for patients who do not respond well to conventional treatments, approximately 10%. Although results are positive there is not yet a formal evidence base for its effectiveness, and as such it is not routinely commissioned for Myasthenia Gravis. Individual Funding Requests (IFR) must be submitted to gain approval. A working group has been established by NHS England to review this process as well as collation of cases and outcome measures to prove efficacy.

The final theme that spanned a couple of presentations was ensuring appropriate communication with patients and that the relevant information is available to them. This was discussed particularly in relation to nutritional support but also care planning for patients with Neuromuscular conditions. The need for definition around what should be included in a care plan and emergency care plan and how they should be used was highlighted. It was agreed that the implications of care planning for Neuromuscular patients should be incorporated within the wider piece of work that the NNAG is undertaking in relation to care planning for all Neurology patients.

The overall feedback from delegates on the day was positive with good participation in discussions and some key areas identified to take forward.

A full write up will shortly be published on the Neurological Alliance website. If you would like more information please contact Lucy Hawkins, Senior Consultant, The Strategy Unit, Lucy.hawkins4@nhs.net.

PREVIEW: Advancing Epilepsy: ILAE British Chapter Annual Scientific Meeting

Join the ILAE at the 2018 International League Against Epilepsy British Chapter Annual Scientific Meeting in Birmingham, UK, from September 26th to the 28th. The 3-day conference features a strong scientific programme with poster and oral presentations focusing on cutting edge basic and clinical research, innovative practice techniques and scientific topics including complex drugs for complex epilepsy, epilepsy and depression: treatment and suicide, gene therapy, understanding seizure spread and studies which will change our practice. In addition, the programme includes the Basic Science Free Communications session, co-hosted by Epilepsy Research UK, and the Birmingham Research and Epilepsy Surgery Network update sessions. The aim is to provide a high quality teaching experience, with the overall objective of improving epilepsy management in Britain.

Submission of abstracts for posters and submissions for two Gower Award categories are invited. The meeting is a great opportunity in which to further your professional development by sharing your research ideas, networking with colleagues and building collaborative relationships. The ILAE British Chapter hope you will attend and find it interesting and instructive. 20 CPD accreditation credits from the Royal College of Physicians have been applied for. ILAE British Chapter members receive discounted registration. Bursaries are also available to attend the meeting. Join the ILAE today, visit www.ilaebritish.org.uk

To learn more and register for the 2018 meeting, visit www.ilaebritishconference.org.uk

PREVIEW: BNOS 2018 Annual Conference

Who are we?

The British Neuro-Oncology Society (BNOS) has its origins in The British Glioma Group (conceived in 1980 as a forum for basic scientists) which became in 1989 The British Neuro Oncology Group, in order to recognise the inclusion of tumours other than glioma, and then The British Neuro-Oncology Society in 2004. By this time, the organisation had widened its coverage to become truly multi-disciplinary, welcoming neurosurgeons, neuro-scientists, neurologists, neuropathologists, neuroradiologists, neuropsychologists, paediatric and adult oncologists, neuropsychiatrists, clinical nurse specialists, radiotherapists, allied health professionals, members of patient and advocacy organisations and many more disciplines.

The Society encourages junior members in all these disciplines by means of dedicated education days and various prizes and awards. BNOS is central to promoting all branches of medicine related to neuro-oncology, leading the way in enhancing both research and clinical practice and uniting all the allied sectors, including Parliamentary and Government. From the earliest days of its predecessor organisations, BNOS has always entertained international figures in neuro-oncology and the Society continues to interact with appropriate national, European and international bodies.

BNOS strives to network neuro-oncology in the following ways:

- By creating opportunities at our annual meetings for effective interaction and collaboration between the diverse neuro-oncology disciplines.
- By fostering specialist education and training for junior scientists and clinicians at our annual Education Day, we strive to encourage young professionals to make neuro-oncology their career of choice.
- We encourage the sharing of innovation in research and clinical practice by offering opportunities for abstract presentations, awards and bursaries.
- Alerting individuals working in the field of neuro-oncology to potential funding opportunities and job vacancies via our website.
- Acting as the voice of neuro-oncology in the political process, promoting increased research funding and up-to-date utilisation of treatments and techniques in clinical practice.

BNOS 2018 Annual Conference
4-6 July, 2018, Winchester, UK

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

The multidisciplinary role of BNOS is represented by plenary presentations, discussions, debates, sponsored symposia, oral presentations and posters covering a wide variety of topics which may range from stem cells and in-vitro models to classification and biomarkers, neuro-imaging and neurosurgical techniques, immuno-oncology, quality of life and indicators of patient performance.

The Wednesday morning will focus on education and research in the field of cerebral metastases. This population of patients is increasing in volume in all of our MDTs and outcomes continue to improve. In the afternoon we will learn about the newly released NICE guidelines for primary and secondary brain tumours and debate the impact and controversies that may result. Following this we will together discuss the management of some more complex and rarer tumours in our MDT meeting, to help us understand different approaches to these challenges.

Thursday will focus on both clinical and scientific aspects of neuro-oncology, with parallel sessions running most of the day. Plenary lectures will educate us on shared decision making and provide a patient and carer perspective from a well known British Actress, Holly Matthews, who has been very active in social media on this subject. We will also learn about the latest surgical techniques and scientific research on paediatric gliomas. We will together celebrate the 70th Birthday of the NHS at the gala dinner!

On Friday we will hear from one of the most experienced oncologists in the field of Proton Beam Therapy from PSI, Switzerland, in the year that PBT arrives in the UK. Our guest from Memorial Sloan Kettering Cancer Centre will explain how we can integrate regenerative stem cell science into cancer research and will have an update on NIHR and brain tumour research in the UK.

Throughout the meeting there will be a number of sessions focusing on presentations of novel work from around the UK and beyond. Prizes will be awarded for the best oral and poster presentations. Bursaries are available from BNOS to attend the meeting.

This year we are delighted to welcome the British Radiosurgery Society who will be hosting an afternoon prior to BNOS conference, that is free to attend and is also accepting abstracts for presentation.

Find out more at: www.bnos.org.uk

Canon Medical Systems UK recognised as carbon zero hero

Thousands of people helped in developing nations as UK patients reap the benefits of innovative medical diagnostic systems.

Canon Medical Systems UK has announced a sustainable milestone offsetting 20,000 tonnes of carbon dioxide (CO2) from ultrasound, X-ray, CT or MRI systems installed into UK hospitals over the past 3.5 years. The scheme means that more than 22,000 people, including 12,000 children, in rural Uganda and Kenya have received practical help to improve mortality, health, quality of life and female empowerment.

Canon Medical Systems is the only UK medical equipment provider to be a Carbon neutral business meeting all PAS2060 requirements by the British Standards Institute. It is now working towards becoming a United Nations Sustainability partner.

The carbon footprint of each Canon Medical Systems imaging product used in the daily prevention, diagnosis and treatment of patients

in NHS and private hospitals has been calculated. This takes into account the elements involved in manufacture, packaging, shipping and average energy usage for the standard lifetime of a system. Each month, UK sales figures are translated into tonnes of carbon and offset to a high impact project in a developing country.

For example, a Canon Medical 1.5T MRI system has a carbon offset footprint of 226.78 tonnes, which then helps 245 people in Kenya and Uganda via cooking stoves and water borehole projects. Cooking on open stoves is a big health issue in developing nations with World Health Organisation figures stating that there are 3.8 million premature deaths per year from non-communicable diseases such as stroke, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and lung cancer.

The Canon Medical Systems UK carbon offset scheme provides 35 modern fuel efficient stoves per MRI system sold. This reduces the amount of smoke particles in a family home, the equivalent to 2 packets of inhaled cigarettes per day. The amount of firewood needed is also halved delivering further environmental and quality of life positives, such as time savings on wood collection so children do not miss school, and lessening deforestation benefiting wildlife habitats and flood prevention.
https://uk.medical.canon

Epistatus® 10mg (in 1ml) oromucosal solution Midazolam available on NHS prescription is approved for use by both the Scottish Medicines Consortium and the All Wales Medicines Strategy Group

Epistatus is licensed for use in the treatment of prolonged, acute convulsive seizures in children and adolescents aged 10 to less than 18 years, who have been diagnosed with epilepsy[1]. Epistatus is presented 'ready-to-use' in a novel, pre-filled, single-dose syringe, in a volume of 1ml, to provide carers with the confidence that they are administering the correct dose[1,2].

Epistatus has been developed specifically for buccal administration. The pre-filled syringe comes in a robust, tamper-resistant pack, which is UV-resistant to maximise shelf life[1]. It is portable and is carried by your patients at all times[2].

The single-dose pack meets the principles of the Medicines Optimisation and NHS RightCare approach to help reduce wastage[3] and is compliant with the Falsified Medicines Directive that will come into force in February 2019[4]. The NHS price for a single 10mg in 1ml pre-filled syringe is £45.76.

Please visit www.epistatus.co.uk for further information about Epistatus 10mg oromucosal midazolam pre-filled syringe, or to find out more about a budget model to calculate the financial impact of prescribing multipack buccal midazolam versus single-pack Epistatus. Prescribing information can be found at https://www.epistatus.co.uk/downloads/epistatus_summary_of_product_characteristics.pdf

References:

1) Epistatus 10mg oromucosal solution. Summary of Product Characteristics.
2) Data on file – Excerpts from Epistatus Patent Application.
3) Medicines Optimisation: Helping patients to make the most of medicines. Royal Pharmaceutical Society May 2013.
4) Pharmaceutical waste reduction in the NHS. NHS England, June 2015.

Acquired Brain Injury Alliance Launches Rehabilitation Prescription Campaign

The Acquired Brain Injury (ABI) Alliance, a collaborative venture between charities, professional groups and industry coalitions working in the field of ABI, launched its Rehabilitation Prescription (RP) Campaign on 1st May.

Speaking at the launch event in London, Professor Michael Barnes, ABI Alliance Chair said: "The Rehabilitation Prescription is a valuable tool that documents the rehabilitation needs of the individual with an ABI. It has no value if the individual with an ABI and their General Practitioner don't receive a copy. And if the individual and the GP don't know what rehabilitation is required then no access to services can be planned or implemented".

The ABI Alliance believes that the RP should be given to every individual, both children, young people and adults with an ABI, on discharge from hospital, with a copy sent to their GP. This will then provide a useful resource for the GP to work with the individual and facilitate access to rehabilitation services in the community, maximising the individual's health outcomes.

The results of the National Clinical Audit October 2016 'Specialist Rehabilitation for Patients with Complex Needs Following Major Injury (NCASRI)' were discussed at the launch. The NCASRI report showed that although all 22 Major Trauma Centres reported that they routinely complete a RP, in one-third of the centres the RP was either sometimes or always given to the patient, but in the remaining two-thirds it was a clinically-held tool.

A Freedom of Information Request was sent last year to all Clinical Commissioning Groups by the United Kingdom Acquired Brain Injury Forum (UKABIF) asking if they logged RPs. The feedback was poor, only four CCGs were positive and recognition of the RP was inexcusably low.
https://www.abialliance.org/

Rett UK

Rett UK is the only UK charity providing professional support to families affected by the rare neurological disorder, Rett syndrome; a severe, life long, life limiting genetic neurological disorder and the most common cause of profound learning disabilities affecting mainly females (1 in 12,000).

Although present at birth, it is usually undetected until a major regression occurs at around two years of age, when children lose acquired skills and the complexity of the disability is revealed.

Rett UK provides emotional and practical support through a national telephone helpline, local family led support groups and a parent-to-parent contact network all so crucial in reducing isolation. Access to high quality seminars from the UK's leading experts on Rett syndrome at our regional events provides families and professionals with up to date, accurate information in subjects like epilepsy, spinal surgery and communication, helping them with management of the disability.
www.rettuk.org

Renishaw neuromate® stereotactic robot assists SEEG procedures

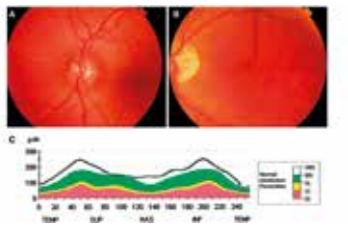
Neurosurgeons at The Walton Centre, Liverpool, UK, have recently carried out their first two stereo-electroencephalography (SEEG) procedures with the assistance of the Renishaw neuromate stereotactic robot. The procedures with a neuromate robot marks a transition to robot assisted neurosurgery.

SEEG is a procedure used in the treatment of epilepsy. Multiple intracerebral electrodes are inserted into the brain in preplanned trajectories to gather data and map brain activity to aim to identify the region responsible for generating epileptic seizures. Once the epileptogenic region has been identified neurosurgeons can follow up with a tailored resection to remove the problematic tissue.

The epilepsy neurosurgery team at The Walton Centre is led by consultant neurosurgeons Professor Paul Eldridge and Mr Jibril Osman-Farah, who estimate that the use of the neuromate robot will reduce procedure times significantly. They commented: "Accurate targeting by multiple electrodes is essential to understand the location of the epileptic focus. Since there are multiple trajectories to be both planned and executed it is highly suited to a robotic system fulfilling the requirement for a repetitive stereotyped activity. Without the robot it becomes impractical to consider such a series of multiple electrodes in a reasonable length of time for the procedure."

By accurately aligning the electrodes according to the neurosurgeons pre-planned trajectory, the neuromate robot helps ensure that neurosurgeons safely reach the targeted anatomy. The Walton Centre was able to acquire the robot through charitable support.

Simple optical imaging technique could provide early diagnosis of rare neurodegenerative disorder



New research published in *Brain* has shown that a cheap, non-invasive test – optical coherence tomography (OCT) – could be key in diagnosing a rare inherited disease called Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS).ARSACS is a progressive neurodegenerative type of ataxia, which is most prevalent in the Charlevoix-Saguenay region of Quebec, Canada, affecting approximately between 1 in 1,500-2,000 individuals. Outside Quebec, ARSACS is rare and the prevalence is unknown.

Study lead Professor Paola Giunti (UCL Institute of Neurology, Head of the Ataxia Centre at UCL/UCLH and a BRC-funded Consultant), and colleague Dr Fion Bremner (also part of the Ataxia Centre), used OCT to test a large group of patients affected by ataxias to see if this test could predict the genetic diagnosis causing ataxia in some patients. The results showed that among the nearly 300 individuals tested with OCT, significant retinal nerve fibre layer thickening was only identified in the 17 ARSACS patients in the study. Patients with other causes of ataxia all had either a normal or thinned retinal nerve fibre layer, providing a sensitivity of 100% and specificity of 99.4% amongst patients affected with ataxias. This is the first time that a test that is not a laboratory-based genetic test has been shown to identify a genetic condition with accuracy.
Read more at http://www.ucl.ac.uk/news/slms/slms-news/slms/simple-optical-imaging-technique-could-provide-early-diagnosis-rare-form-neurodegenerative-disorder

NICE issues guidance on disease modifying therapies for multiple sclerosis

The National Institute for Health and Care Excellence (NICE) has issued its Final Appraisal Determination (FAD) recommending the use of four out of six disease-modifying therapies (DMTs) in relapsing-remitting multiple sclerosis. Rebif® (interferon β-1a), Avonex® (interferon β-1a), Extavia® (Interferon β-1b) and Copaxone® (glatiramer acetate) have been recommended, within their marketing authorisations, as options for treating relapsing-remitting multiple sclerosis in the NHS provided the companies provide the drugs with the discounts agreed in the patient access schemes. NICE does not recommend Betaferon® (interferon β-1b), concluding that it would not be a good use of NHS resources. NICE has also stated it is not in a position to recommend pegylated interferon β-1a (Plegridy®) and that there will be a separate single technology appraisal for this drug. These recommendations are not intended to affect treatment with a beta interferon or glatiramer acetate that was started in the NHS before this guidance was published.

The National Institute for Health and Care Excellence (NICE) have been appraising the clinical and cost-effectiveness of beta interferons (interferon β-1a (Avonex®, Rebif®), Pegylated interferon β-1a (Plegridy®), and interferon β-1b (Betaferon®/Extavia®) and glatiramer acetate (Copaxone®) in multiple sclerosis, against best supportive care, in the context of a multiple technology appraisal.

The recent FAD follows a preliminary decision in December 2017 to recommend only Extavia® (interferon β–1b) as an option for treating multiple sclerosis.

The Brain & Spine Foundation launches new website

The Brain & Spine Foundation charity has launched a new website, which meets the highest standards of accessibility and is more responsive to mobile devices. The Brain & Spine Foundation produces booklets and fact sheets on over 25 neurological topics. The charity distributed over 100 thousand online and hard copies of its publications in 2017. The previous website's directory of neurological topics has been revamped and expanded into a more comprehensive index, containing more information on a number of tests, treatments and conditions. A new section is dedicated to connecting with healthcare professionals, and provides information on educational events and continued professional development opportunities in order to improve the quality of care and support received by neurology patients. *www.brainandspine.org.uk*

For your eligible patients with NVAF:

ONCE-DAILY LIXIANA®▼ (edoxaban)

- Superior reduction in major bleeding vs. well-managed warfarin[1]
- Proven efficacy – Comparable to well-managed warfarin in the prevention of stroke/SEE[1]
- Simple & convenient – Once-daily dosing, with or without food – consistent across both NVAF and VTE indications[2*]

RECOMMENDED BY NICE AND SMC ACCEPTED[3,4]

The primary safety endpoint was the incidence of adjudicated major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH)[1,5]

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

once-daily Lixiana™ edoxaban

Indicated for:[2]

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

LIXIANA▼ (edoxaban) 60mg/30mg/15mg film coated tablets
See summary of product characteristics prior to prescribing for full list of adverse events

Presentation: 60 mg (yellow) / 30 mg (pink)/ 15mg (orange) edoxaban film coated tablets (as tosilate). **Indications:** 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) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology and method of administration:** *NVAF* -The recommended dose is 60 mg edoxaban once daily with or without food. Therapy with edoxaban in NVAF patients should be continued long term. *VTE* - The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days with or without food. Duration of therapy (at least 3 months) should be based on risk profile of the patient. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min), low body weight ≤ 60 kg and / or concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. The 15 mg dose of edoxaban is not indicated as monotherapy, and should only be used during a switch from edoxaban to VKA (see SmPC for full details). Edoxaban can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram guided cardioversion in patients not previously treated with anticoagulants, edoxaban should be started at least 2 hours before cardioversion to ensure adequate anticoagulation. Cardioversion should be performed no later than 12 hours after the dose of edoxaban on the day of the procedure. Confirmation should be sought prior to cardioversion that the patient has taken edoxaban as prescribed. If a dose of edoxaban is missed, the dose should be taken immediately and then continued once daily on the following day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal (GI) ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Uncontrolled severe hypertension. Concomitant treatment with any other anticoagulants e.g. UFH, low molecular weight heparins, heparin derivatives (fondaparinux, etc.), VKA or NOACs except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Pregnancy and breast-feeding. **Special warnings and 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. Haemodialysis does not significantly clear edoxaban. Renal impairment: Renal function should be assessed prior to initiation of edoxaban and afterwards when clinically indicated. Not recommended in patients with end stage renal disease or on dialysis. Renal function and NVAF: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful benefit risk evaluation. Hepatic impairment: Not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment. Edoxaban should be used with caution in patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN. *Surgery or other interventions*: discontinue edoxaban at least 24 hours before the procedure. If the procedure cannot be delayed, the increased risk of bleeding should be weighed against the urgency of the procedure. Edoxaban should be restarted as soon as haemostasis is achieved. *Prosthetic heart valves and moderate to severe mitral stenosis*: Not recommended *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy*: Not recommended *Patients with active cancer*: Not recommended. **Drug interactions:** The *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole result in increased concentration of edoxaban and a dose reduction of 30mg is required. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. phenytoin, carbamazepine, phenobarbitol or St John's Wort). Concomitant high dose ASA (325mg) or chronic NSAIDs is not recommended. **Undesirable effects:** Common: anaemia, dizziness, headache, epistaxis, abdominal pain, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gamma GT increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal. Uncommon: hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. Rare: anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Legal category: POM Package quantities and basic NHS costs: 60mg / 30mg – 28 tablets £49.00 15mg – 10 tablets £17.50 Marketing Authorisation (MA) number: EU/1/15/993/001-16 MA holder: Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 Munich, Germany**

Date of prep of PI: July 2017 | EDX/17/0140

Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to Daiichi Sankyo UK Medical Information on 0800 028 5122, medinfo@daiichi-sankyo.co.uk

References: 1. Giugliano RP *et al. N Eng J Med* 2013;369(22):2093–2104. **2.** LIXIANA® Summary of Product Characteristics. **3.** NICE Technology appraisal guidance [TA355]. September 2015. **4.** Scottish Medicines Consortium advice. SMC No. (1095/15). October 2015. **5.** Schulman S *et al. J Thromb Haemost* 2005;3(4):692–694.

www.lixiana.co.uk

Daiichi-Sankyo