ISSN 1473-9348 VOLUME 13 ISSUE 6 NOVEMBER/DECEMBER 2013

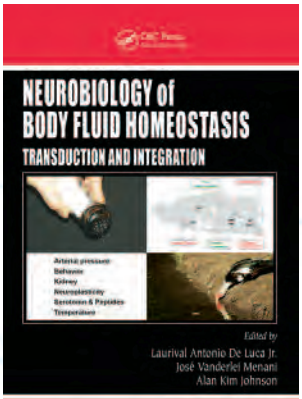
ACNR

www.acnr.co.uk

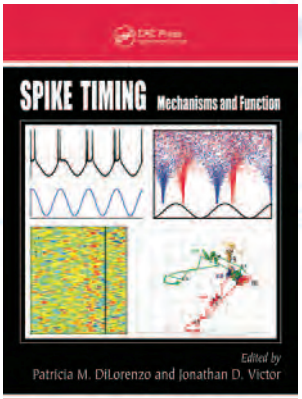
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

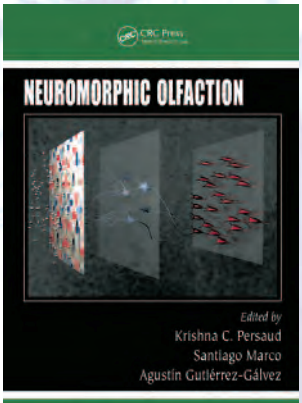
Frontiers in Neuroscience
from CRC Press



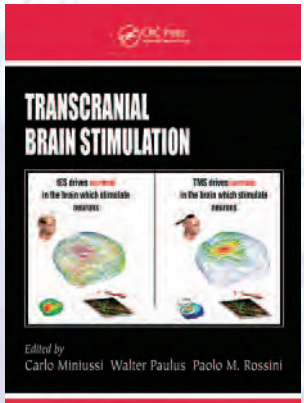
Neurobiology of Body Fluid Homeostasis: Transduction and Integration
October 2013 | 336pp
9781466506930 | £89.00



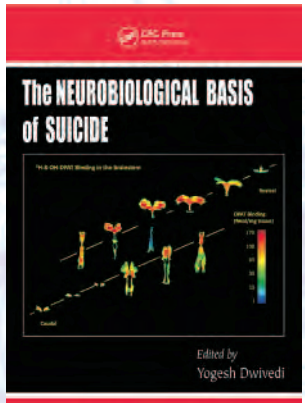
Spike Timing: Mechanisms and Function
May 2013 | 442pp
9781439838150 | £95.00



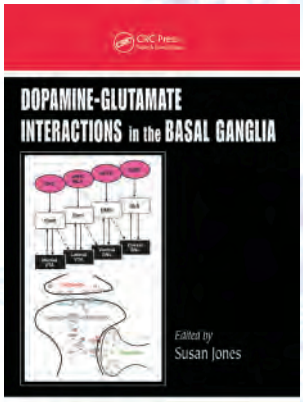
Neuromorphic Olfaction
April 2013 | 238pp
9781439871713 | £95.00



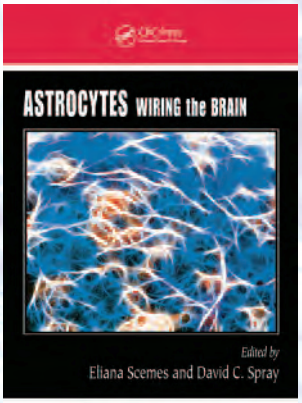
Transcranial Brain Stimulation
December 2012 | 465pp
9781439875704 | £99.00



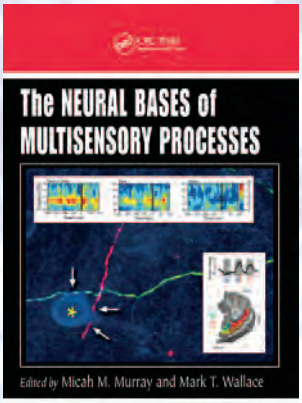
The Neurobiological Basis of Suicide
June 2012 | 482pp
9781439838815 | £95.00



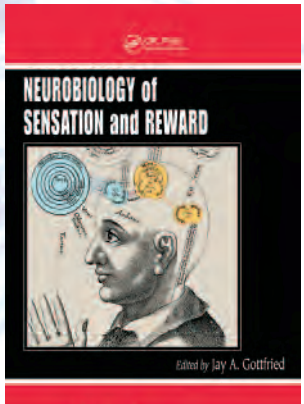
Dopamine – Glutamate Interactions in the Basal Ganglia
December 2011 | 284pp
9781420088793 | £101.00



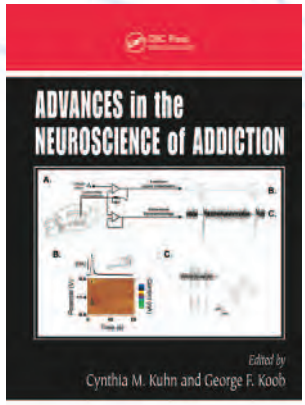
Astrocytes : Wiring the Brain
November 2011 | 440pp
9781439825846 | £101.00



The Neural Bases of Multisensory Processes
August 2011 | 809pp
9781439812174 | £101.00



Neurobiology of Sensation and Reward
March 2011 | 466pp
9781420067262 | £101.00



Advances in the Neuroscience of Addiction
April 2010 | 238pp
9780849373916 | £97.00

20% discount when you order online and enter discount code

LBM18 at checkout

Expires 31/12/2013

FREE standard shipping when you order online.

w w w . c r c p r e s s . c o m

CONTENTS

NOVEMBER/DECEMBER 2013

Cover shows image taken on the MAGNETOM Prisma 3T MR system from Siemens Healthcare, recently presented at RSNA.

ACNR

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

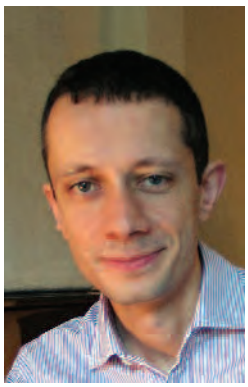
ADVERTISING
Rachael Hansford
T. 01747 860168 M. 07989 470278
E. rachael@acnr.co.uk

COURSE ADVERTISING
Cathy Phillips E. Cathy@acnr.co.uk

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

PRINTED BY
Buxton Press T. 01298 21 2000

Bookmark
www.acnr.co.uk
for exclusive
online content



Mike Zandi, Editor.

In this issue we have the first of an excellent series of articles on Stroke Medicine, organised by our guest editor David Werring, from the Stroke Research Group at Queen Square and Reader in Clinical Neurology at the UCL Institute of Neurology. Dr Werring introduces the series on page 21. We are lucky to have Dafydd Thomas, and three of the original members of the Queen Square cerebral blood flow (CBF) group, John Marshall, Ralph Ross Russell, and Lindsay Symon, write about the British contribution to Stroke Medicine in the 20th Century. It is inspiring to read about how old precepts, for instance the vasospasm or insufficiency theories of transient ischaemic attacks, were overcome and how these authors and others they mention changed clinical practice in several ways for the better. We hope you enjoy the rest of the articles in this series to come.

Hearing loss is highly prevalent, and congenital hearing loss and age related hearing loss are both big problems. Karen Steel from King's College London and the Wellcome Trust Sanger Institute, Hinxton, where she has established the Mouse Genetics Programme, reviews the genetics of hearing loss, including genetic risks for susceptibility to the damaging effects of drugs (e.g. mitochondrial A1555G and aminoglycosides), mutations affecting cochlea function and the advances made from studying mutant mice.

James Shine and Simon Lewis, from Sydney, review the neuroimaging evidence for the pathophysiology of visual hallucinations in Parkinson's disease being centred on dysfunction in attention. Specifically, there may be a breakdown in communication between neuronal networks subserving attention. These mechanisms may underlie visual hallucinations in other disorders, and so the insights from this work may be considerable and help develop therapies.

Are virtual reality based therapies feasible in the real world of neurorehabilitation? Madeleine Grealy and Bilal Nasser from Strathclyde provide a compelling account of the evidence for the techniques and justifications for their use. Analgesic associated chronic headache was first described in the 1950s yet still represents a large proportion of the workload in general neurology clinics. Zaza Katsarava and Mark Obermann from the Essen Headache Centre, in Germany, write on this common problem and provide a helpful account of the specifics of the condition and approaches to treatment. In one cited study, basic patient education seemed to be as effective as a programmed detoxification programme. In our epilepsy article, Christine Bennett from Leeds and Helen Cross from UCL describe the particular challenges in guiding emergency rescue therapy for children with prolonged seizures in the community, emphasising the views of epilepsy specialist nurses and the need for stronger links with schools.

What do you consider the paper of the year in neurology in 2013? Gemma Cummins in our journal reviews section this issue has rounded up reviews of the 'paper of the year' from several notable authors in this issue, covering demyelination, genetic ataxia, Guillain Barré syndrome, rehabilitation, motor neurone disease, tic disorders, epilepsy and stroke. We are delighted to have Andrew Larner write for us again, in what have often been the most popular of ACNR's articles since the beginning of this journal. In this issue he provides an account of echolalia and synaesthesia in the works of F Scott Fitzgerald (1896-1940) and Kurt Vonnegut (1922-2007). We hope you enjoy this issue and please contact us if you would like to contribute to the journal.

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

DESITIN
SUCCESS IN CNS

It's the small things that can make a difference

NEW

Desitrend®

Levetiracetam minitablets

Epilepsy therapy in an intelligent form

A formulation with benefits for both patients and payers

- Unique minitablet formulation
- Bioequivalent to the leading brand of levetiracetam[1]*
- Improved seizure control and adherence in patients switched from conventional levetiracetam tablets[2†]
- Single site of manufacture[3]
- **20% lower cost** than leading branded levetiracetam[4]*

**Keppra® †Non-interventional study*

The authors of an 8-week, non-interventional study in 395 patients concluded that Desitrend® minitablets have the potential to bring about **lasting improvement in patient compliance:**

*"…and to **improve the efficacy** of long-term treatment in patients."*[2]

Prescribing information can be found opposite.

Indication: Monotherapy of partial seizures in patients ≥16 years of age with newly diagnosed epilepsy.
Please consult the Summary of Product Characteristics for full indication and dosing instructions.

Editorial board and contributors

Life Time Achievement Award

Congratulations to Franz Gerstenbrand who was presented with a Life Time Achievement Award during the World Congress of Neurology in Vienna in September.

Franz Gerstenbrand who was born in south Moravia was accepted for training in neurology in 1950. His career led him to become head of the Neurological University Clinic in Innsbruck. He was also responsible for the implementation of a stroke unit long before these units were obligatory for most neurological departments in Austria or abroad, as well as a neurological CT department, a highly specified chemical laboratory and a neurological intensive care department.

Foulkes Foundation Medal Winner 2013 announced

The 2013 Foulkes Foundation Medal, which recognises outstanding early career biomedical researchers has been awarded by the Academy of Medical Sciences to Dr Akhilesh Reddy, a neuroscientist at the Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge.

The Foulkes Foundation Medal recognises a rising star in biomedical research for making a significant impact on UK bioscience within ten years of finishing their PhD.

The winner will receive the Medal and a cash prize of £1500, and will deliver a lecture on their research at the Academy's annual Spring Meeting for Clinician Scientists in Training.

Dr Reddy is a Wellcome Trust Senior Clinical Research Fellow, whose research focuses on the role of circadian rhythms in the brain. It explores how disruption of this clockwork programming through old age, neurological disease, and even shift-work can impact on health and life expectancy. He is specifically working on the role of sleep dysfunction in patients with neurodegenerative conditions such as Parkinson's disease.

Alzheimer's Research UK grants Bath scientist funds for new dementia study

Dr Giordano Pula from the University of Bath's Department of Pharmacy & Pharmacology has been awarded £29,000 by Alzheimer's Research UK to study vascular complications of Alzheimer's disease.

The study, funded by the UK's leading dementia research charity, aims to understand how blood cells and blood vessels can be affected during the disease and to shed light on why people with Alzheimer's also seem more prone to vascular problems, such as stroke. The work will be carried out in collaboration with Dr Ilaria Canobbio and Professor Mauro Torti from the University of Pavia (Italy).

The researchers will study how amyloid interacts with platelets, the circulating cells responsible for blood clotting, and the lining of our blood vessels. In particular, they will study whether presence of amyloid makes platelets clot more readily.

To feature your awards news here, Email Anna@acnr.co.uk

Merck Serono Showcases Its Commitment to Multiple Sclerosis: Supports the Grant for Multiple Sclerosis Innovation and the Multiple Sclerosis Resource Centre Website

Grant for Multiple Sclerosis Innovation

In October 2012, Merck Serono announced the launch of the Grant for Multiple Sclerosis Innovation (GMSI) – a grant worth up to a million Euros for projects by academic researchers aimed at developing scientific breakthroughs and collaborative approaches to improve the lives of multiple sclerosis (MS) patients. The committee received as many as 112 applications from across the globe, with projects addressing several different aspects of MS, including risk, prognosis and potential novel treatments.

For the occasion of the 29th European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the company announced the recipients of the inaugural GMSI. "At Merck Serono, we recognize the value of a broad R&D ecosystem, and seek to lever insights and expertise from across the continuum of the healthcare landscape," says Dr. Annalisa Jenkins, Executive Vice President and Global Head of Research and Development at Merck Serono. "The Grant for MS Innovation is a unique platform which will help us to accelerate exceptional science that exhibits the potential to become an innovative medicine or a high-value solution for patients. By investing in these research opportunities, we are building a bridge to a future in which more therapeutic options will improve the quality of life for those living with multiple sclerosis."

Four recipients, three from the United States and one from Germany, will share the overall one million Euros grant to support their research. Here are the winners of the award:

- **Dr. Daniel Harrison, Assistant Professor of Neurology** at the Johns Hopkins University School of Medicine, received a grant for research seeking to translate novel magnetic resonance imaging and analysis techniques into tools that have clinical applications in MS. He is focused on the validation of tools that will provide more pathologically specific assessments in future clinical trials.
- **Dr. Thomas Thum, Professor and Director of the Institute of Molecular and Translational Therapeutic Strategies** at Hannover Medical School (Germany), previously evaluated whether microRNAs are differentially regulated in the cerebrospinal fluid (CSF) of patients with MS. The awarded grant will allow him and a network of German centers to validate their initial findings of altered microRNA patterns in the CSF of up to 1000 patients with MS.
- **Dr. Kevin O'Connor, Assistant Professor of Neurology** at Yale School of Medicine, studies immunology and neurology. His laboratory is specifically interested in defining the mechanisms by which immune cells called B cells, and the antibodies they produce, influence tissue damage in autoimmunity. The grant will be used to support work in determining the specificity of autoantibodies and understanding how particular types of B cells initiate and sustain autoimmunity.
- **Dr. Joshua Bacon, Chair of the Department of Psychology** at Stern College for Women at Yeshiva University in New York City, research scientist in the Department of Neurology of the NYU School of Medicine, and member of the clinical and research team in the NYU Multiple Sclerosis Care Center, will use the grant to support his research developing tests to detect speed-of-processing impairments in sub-clinical and early MS and developing a comprehensive cognitive rehabilitation program for patients with MS who have cognitive impairments.

Figure. Andrew Galazka (Merck Serono), Dr. Kevin O'Connor, Prof. Maria Trojano, Dr. Thomas Thum, Dr. Daniel Harrison & Prof. David Bates

Grants will be awarded annually moving forward. The second call for proposals, for the 2014 GMSI was made by Merck Serono during the award ceremony at ECTRIMS. The awards symposium was co-chaired by David Bates and Maria Trojano. Dr Bates is Emeritus Professor of Clinical Neurology at the University of Newcastle upon Tyne, UK, and a member of the GMSI Scientific Committee. Professor Trojano is Professor of Neurology and Chief of the Neurophysiopathology Unit at the University of Bari, Italy. She is Vice President of the ECTRIMS Executive Committee and a scientific committee member of many MS organizations, including the Italian National MS Society. More information about the GMSI can be found at the following website: ***www.grantformultiplesclerosisinnovation.org***.

Multiple Sclerosis Resource Centre

Additionally and also during the ECTRIMS congress, Elsevier's new MS Resource Centre was launched (http://multiplesclerosis.elsevierresource.com). The MS Resource Centre is a medical education platform for healthcare providers hosted by Elsevier's new peer-reviewed journal, Multiple Sclerosis and Related Disorders (http://***www.msard-journal.com/)***. The website will afford the MS community numerous benefits, including access to taped lectures, video interviews with leaders in the field, a congress planner and key articles reporting on breakthrough findings by highly regarded authors. Timothy Vartanian, MD, PhD, Professor at the Brain and Mind Research Institute and the Department of Neurology, Weill Cornell Medical College, Cornell University is the Editor of the Resource Center.

Merck Serono is the founding supporter of the MS Resource Centre website and helped establish it through an unrestricted grant to Elsevier, B.V. "Merck Serono is proud to have provided the necessary foundation for Elsevier to develop this website that aims to provide clinicians with access to the latest literature on multiple sclerosis" said Thorsten Eickenhorst, MD, PhD, MBA, Senior Vice President and Chief Medical Officer at EMD Serono, Inc., a subsidiary of Merck KGaA, Darmstadt, Germany. "We are committed to supporting organizations that invest in the understanding and treatment of multiple sclerosis, and share our goal of improving patient care."

This article was supplied by Merck Serono and they have paid for its inclusion in ACNR

PAPER OF THE YEAR: MULTIPLE SCLEROSIS

Chosen article: ***Sodium Chloride Drives Autoimmune Disease by the Induction of Pathogenic Th17 Cells. Kleinewietfeld M, Manzel A, Titze J et al. Nature 2013;496:518-52.***

Reviewer: Dr Alasdair Coles, Senior Lecturer University of Cambridge & Honorary Consultant Neurologist, Addenbrookes Hospital, Cambridge.

Multiple Sclerosis and salt

2013 has been the Year of Salt for multiple sclerosis. The high-brow gossip is no longer about vitamin D or veins, but humble sodium chloride.

For several years, Ken Smith and colleagues in London have been assembling a picture of the metabolic life of the demyelinated axon. It turns out that the innocent sodium ion, Na^+, can be a millstone around the neck of the struggling axon. As a nerve demyelinates, sodium channels spread from the nodes of (Louis-Antoine) Ranvier to redistribute along the length of the naked axon. So, when Mr Hodgkin and Mr Huxley's action potential passes by, there is rather more sodium entry to the cell than there should be. The more sodium ions accumulate inside the axon, the more energy is required to get rid of them, and someday energy supply cannot meet demand and the lights go out. This can even be imaged: David Miller showed this sodium accumulation in people with progressive multiple sclerosis radiologically in Brain this July.

The news this year is that eating salt is bad for multiple sclerosis. David Hafler's team at Yale have shown that naïve T cells can be turned into nasty killer Th17 cells by swimming in salty water. Furthermore, mice who eat salty food (?) are particularly susceptible to experimental autoimmune encephalomyelitis (EAE), because bad Th17 cells have been switched on.

Why should salt have this effect? Well, lymph nodes normally have high salt levels; perhaps this activates Th17 cells, while they encounter antigen, and then the cells calm down in the lower-salt environments outside the node.

Should people with multiple sclerosis go on a low-salt diet? Well probably, to avoid hypertension and the like. But it is a little early to deny our patients the important morale-boosting effects of salted battered cod and chips.

PAPER OF THE YEAR: GENETICS IN ATAXIA

Chosen article: ***Ataxia, Dementia and Hypogonadotropism Caused by Disordered Ubiquitination. Margolin DH, Kousi M, Chan YM et al. The New England Journal of Medicine 2013;368:1992-2003.***

Reviewer: Dr Sarah Wiethoff, Dr Joshua Hersheson and Prof Henry Houlden, Department of Molecular Neuroscience and MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London.

The Quickening Maze

Gordon Morgan Holmes first described the co-occurrence of cerebellar ataxia and hypogonadism in 1907 as a neurologist at The National Hospital for Neurology and Neurosurgery in London. Over 100 years later in 2013 a gene was identified causing a very similar phenotype of "Ataxia, Dementia and Hypogonadotropism Caused by Disordered Ubiquitination" by Margolin et al. published in *The New England Journal of Medicine*.

Using whole-exome sequencing and consecutive targeted sequencing of candidate genes Margolin et al identified digenic homozygous mutations in RNF216 and OTUD4, encoding two proteins in the ubiquitination pathway, in three affected siblings with consanguineous background. Compound heterozygous truncating mutations in RNF216 could be found in one additional unrelated patient as well as single heterozygous deleterious mutations in four other patients. The clinical phenotype comprised hypogonadotropic hypogonadism with defects at the hypothalamic and pituitary levels of the endocrine axis, as well as progressive ataxia and dementia with neuronal loss in cerebellum and hippocampus. Functional knockdown of the single genes and the combination of both induced a similar phenotype in zebrafish which could be rescued by nonmutant human RNF216 or OTUD4 messenger RNA. Ubiquitin-immunoreactive intranuclear inclusions were present in surviving hippocampal neurons.

The study sheds important light on the genetic underpinnings of the association of ataxia with hypogonadotropic hypogonadism by showing that mutations in RNF216 either solely or combined with mutations in OTUD4 can cause this clinical phenotype that was previously genetically unresolved. The published release of these two new genes prompted us to screen our clinical cohort of unresolved autosomal-recessive cerebellar ataxias for further affected cases. Surprisingly we identified a homozygous splicing variant in RNF216 in a patient with early adulthood-onset cerebellar ataxia from a consanguineous family which segregated within the family and was neither found in our in-house database of 300 exomes nor in the conventional open access exome databases. Interestingly, our patient did not have hypogonadotropic hypogonadism, nor dementia.

The description of two causal genes in the constellation of syndromes comprising ataxia, dementia and hypogonadotropism will open pathways further elucidating the importance of disordered ubiquitination in neuronal degeneration. Nonetheless, our findings show that even though the current study of Margolin et al. is solidly backed-up by functional data, one needs to remain open to the possibility of further phenotypic variability within the spectrum of ataxia and ubiquitination disorders.

PAPER OF THE YEAR: GUILLAIN BARRÉ SYNDROME

Chosen article:

- ***Jacobs BC. IGOS - International GBS Outcome Study***
- ***International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. Dodd CN, Romio SA, Black S, et al. Vaccine 2013;31:4448–58.***
- ***IGOS Newsletter. https://www.gbsstudies.org/extended-newsletter***

Reviewer: Dr Simon Rinaldi, Academic Clinical Lecturer, Nuffield Department of Clinical Neurosciences, University of Oxford.

GBS: Strength in numbers

My paper of the year review includes one paper, two clinical trials, and a multi-centre observational study, united under the common theme of the year in Guillain Barré syndrome – international collaboration.

Ever since the 1976 "swine flu" vaccine was suspected of inducing GBS there have been anxieties that subsequent vaccines might also have this adverse effect. This was especially the case during the contemporary outbreak of a similar influenza strain (H1N1). In a study published earlier this year, the Global H1N1 GBS Consortium demonstrate the feasibility of international collaboration in assessing vaccine safety. An impressive 479 GBS cases were contributed by 15 countries, providing unprecedented power to assess this rare adverse event. Using a self-controlled case series methodology not reliant on accurate knowledge of underlying background incidence rates, the consortium report a relative increased incidence risk of 2 to 3 for GBS in the 42 days following H1N1 vaccination, translating to 1-2 excess cases per million vaccines administered. They were also able to show the time of peak GBS risk is 8-21 days post vaccination, as might be expected for a pathological mechanism likely to be driven by an IgG based humoral immune response. The at risk period chosen and the influence of seasonal infections, including influenza itself, can confound these estimates. Nevertheless, the study addresses these concerns using a number of different statistical approaches, and gives a consistent estimate of the risk of vaccination with respect to GBS. This has immediate utility in counselling patients who might receive vaccination, and in informing vaccination policies.

The bottom line is that this high quality evidence shows that the risk of GBS is low, and almost certainly outweighed by the protective benefits of vaccination.

Likewise, patients with GBS are often understandably anxious to know how long they will take to recover. Until recently, meaningful prognostication proved difficult. Another highly impressive ongoing international study aims to identify easily obtainable factors which

predict disease course at an early stage, building upon earlier excellent work from the Dutch GBS study group. The International GBS Outcome Study (IGOS) aims to collect detailed clinical data, along with serum samples and DNA, from 1000 patients with GBS. In the last year 100 centres over 13 countries have joined the study and approaching 220 patients have been included at the time of writing. This unprecedented international collaboration has great promise in improving prognostication, but also will provide an extremely valuable bio-bank for studying immunopathological mechanisms and genetic susceptibility. Moreover, IGOS will integrate with international multi-centre treatment trials, as has already begun with the International Second IVIg dose trial, and will underpin future studies of novel agents such as complement inhibitors.

The benefit of international collaboration for addressing key questions in GBS has already been well demonstrated, and as such the results from IGOS and related studies are eagerly anticipated. They seem likely to feature prominently in future 'paper of the year' reviews.

PAPER OF THE YEAR: NEURO REHABILITATION

Chosen article: ***Early cranioplasty may improve outcome in neurological patients with decompressive craniectomy. Bender A, Heulin S, Röhrer S et al. Brain Injury 2013;27:1073-1079.***

Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust.

Cranioplasty – What are you waiting for?

The neurosurgical management of patients sustaining intracranial hypertension in the context of traumatic brain injury or stroke may involve decompressive craniectomy. The removal of part of the skull in order to prevent secondary brain damage through increasing intracranial pressure is no longer the esoteric procedure that it was once seen as. Because the procedure is almost always performed in emergency situations, the availability of well-planned double-blinded trial data is obviously somewhat limited. It is difficult, therefore, to apply a sound evidence base to decisions made in the acute environment on an individual patient basis.

Those who come through neurosurgical services having undergone a craniectomy may then undergo a cranioplasty, which involves either replacing the original skull flap which was removed or a titanium plate, fashioned specifically to cover the defect. Different neurosurgeons have different views around the timing of cranioplasty. Although some patients do develop sunken bone flaps with deteriorating neurological function secondary to shifts in intracranial contents, there is very limited information on the optimal timing for replacement of the flap and this remains a source of some frustration for patients and clinicians. The rather crude outcome measures employed in many surgical studies do not capture any meaningful change in consciousness levels following the procedure and it is seen as being of rather low-priority in the ongoing management of this patient group. There are many anecdotal reports and case series of significant improvements being engendered by undergoing cranioplasty, but very little outcome data on larger populations.

This German series follows 147 patients undergoing inpatient neurological rehabilitation who are, therefore, subject to regular clinical scrutiny and assessment. The series compares patients undergoing early (<86 days) and late (>86 days) cranioplasty in terms of their Barthel Index (BI), Functional Independence Measure (FIM) and Coma Responsiveness Scales (CRS). It is illuminating that the two groups were allocated operative intervention at times determined by "organisational issues and surgeon choice" rather than any specific clinical factor.

There was no difference in pre-operative functional level (BI) or age between the groups. Patients undergoing early (<86 days) cranioplasty had significantly better BI ($p<0.01$) and FIM ($p<0.05$) scores than the late intervention group at the time of discharge from inpatient rehabilitation. There were no differences in levels of awareness (CRS) at discharge. For all patients undergoing cranioplasty there were significant immediate improvements in function following the procedure as evidenced by gains in the BI ($p<0.001$) and FIM ($p<0.001$) in the first week afterwards. There were no differences in complication rate (bleeding, seizures, infection, stroke) between the 2 groups.

Unfortunately no mention is made of the effect on length of stay in rehabilitation or of the larger economic and social implications of functional improvements engendered by earlier intervention. Nevertheless, it does go some way to asserting what many professionals working in brain injury rehabilitation have suspected for some time; that postponing and delaying elective cranioplasty as a low priority procedure is clinically questionable.

PAPER OF THE YEAR: CLINICAL ASPECTS OF MND

Chosen article: ***Structural brain network imaging shows expanding disconnection of the motor system in amyotrophic lateral sclerosis. Verstraete E, Veldink JH, van den Berg LH et al. Hum Brain Mapp. 2013 Mar 1 [Epub ahead of print].***

Reviewer: Dr Martin R. Turner, MRC Senior Clinical Fellow and Honorary Consultant Neurologist, University of Oxford Nuffield Department of Clinical Neurosciences & John Radcliffe Hospital, Oxford.

ALS Imaging: An elegant model

At the time of writing, more than 1300 articles have been published with a 2013 date using the PubMed search term 'amyotrophic lateral sclerosis (ALS) or motor neurone disease'. The total for the year is expected to exceed 2000, and already represents more than 5% of the total number of publications in this field. An exponential growth in ALS research has been driven by advances in the understanding of the molecular biology, in particular the role of aberrant cellular RNA processing and protein handling. ALS shares clinical, pathological and now genetic features with frontotemporal dementia (FTD), with hexanucleotide repeat expansions in C9orf72 associated with nearly 10% of all apparently sporadic ALS and 25% of 'pure' FTD cases. The traditional concept of ALS involving a highly selective vulnerability of only upper and lower motor neurons is now untenable. ALS is a multiple system disorder in which the brain is consistently involved.

Beyond advances at the cellular level, there is a growing realisation that to fully understand the pathogenesis of neurodegenerative disorders, not least how they are propagated in such stereotyped clinical patterns, requires the study of the brain and its downstream connections as a system. The development and analysis of resting-state functional MRI-defined networks is a growing area in this regard, but an allied strategy has been to apply network mathematical theory to the detailed white matter tract connectivity maps that may now be derived entirely non-invasively from diffusion tensor imaging (DTI).

Graph theory is based on 18th Century Swiss mathematician Leonhard Euler's solution to the Seven Bridges of Königsberg problem. The brain may be represented as a system of hubs (nodes or vertices), linked by tracts (edges or lines) defined using well-established tractographic techniques based on DTI data. The team from Utrecht, Netherlands applied this technique to twenty-four ALS patients scanned twice with a six-month interval, and compared to healthy controls. The paper initially elegantly outlines several possibilities for how their model consisting of 83 nodes and edges might change over time (Figure 1). Rather than the dogma of ALS pathology affecting only a fixed set of primary motor connections, their results demonstrate an expanding network of impaired connectivity over time, with notable involvement of frontotemporal lobe projections, entirely in keeping with clinical, histopathological and molecular insights.

The nature of spread of neurodegeneration is unclear, but a "prion-like" propagation between neurons is a candidate mechanism. The observation clinically and histologically of contiguous regional involvement in body territories certainly supports the view that structural connectivity is important in

defining this process in ALS, and the authors conclude that their results are consistent with this concept.

MRI has come a long way from greyscale histological images, and the "just a pretty picture" dismissal of DTI is entirely unjustified. Of course the validity of applying mathematical models, in particular graph theory, to biological systems as complex as the brain is highly questionable. The brain is clearly not an 83-node structure, and it will be challenging to find ways to validate such models. Clinical observations in conjunction with neurophysiological correlates (e.g. MEG) and traditional histopathological study, including the emerging field of post mortem DTI, offer potential.

These connectivity studies are not yet applicable to the single subject. However, I believe we have glimpsed the future of neuroimaging, particularly "systems-level neuroscience" in this article. A paradigm shift in the concept of neurodegeneration is underway, which will crucially include application of these techniques to pre-symptomatic individuals at high genetic risk. Advanced MRI is now at the forefront of the search for much-needed biomarkers that will be essential for the goal of a therapeutic era in ALS.

PAPER OF THE YEAR: PATHOGENESIS OF MOTOR NEURON DISEASE

Chosen article: ***Unconventional Translation of C9ORF72 GGGGCC Expansion Generates Insoluble Polypeptides Specific to c9FTD/ALS. Peter E.A. Ash, Kevin F. Bieniek, et al. Neuron 2013; 77:639–46.***

Reviewer: Professor Kevin Talbot, Nuffield Department of Clinical Neurosciences, University of Oxford.

Zooming in on C9orf72

Our understanding of the cause of two important neurodegenerative diseases underwent a step change in 2011 with the identification of an expanded hexanucleotide (GGGGCC=G4C2) repeat in the first intron of the C9orf72 gene as the most common mutation in familial ALS and FTD patients. Remarkably, as well as affecting 30-40% of familial ALS, FTD and ALS/FTD cases, the mutation is found in 7% of sporadic cases of ALS and 6% of FTD. Pathologically, C9orf72 mutation cases have TDP-43 positive inclusions, like those found in the majority of ALS and FTD-TDP patients, but also have atypical TDP43-negative inclusions. Since then the mechanism of toxicity of this mutation has been the subject of intense interest. As with myotonic dystrophy nuclear RNA foci can be detected using a probe against the G4C2 and the leading theory behind cellular toxicity is still therefore that these RNA foci bind ribonuclear proteins, interfering with post-transcriptional mRNA processing, presumably of genes with neuronal specificity. Other evidence, principally morpholino-induced knockdown in zebrafish, suggests that reduced levels of the C9orf72 protein, the function of which is currently unknown, might play a part in pathogenesis.

A third potential mechanism is suggested by a study reported in *Neuron* in 2013, implicating a novel kind of protein toxicity. The authors took the elegant approach of studying the repetitive sequence in the G4C2 expansion and hypothesizing that, although the expansion is in a non-coding part of the gene, the potential products of a non-canonical form of translation previously observed in other repeat disorders (SCA8 and myotonic dystrophy). Repeat associated non-ATG (RAN) translation is predicted to generate a series of dinucleotide repeat proteins, the number and variety of which depend on the frame in which translation occurs. To test this hypothesis they generated polyclonal antibodies by injecting GA, GP, and GR (glycine+alanine, proline or arginine) octamers as antigens, from the predicted RAN translation products of (GGGGCC)n transcripts in the three alternate reading frames. The resulting harvested serum was used to probe tissue from FTD and ALS patients and detected specific immunoreactivity, not present in other neurodegenerative disease. This highly novel and unexpected mechanism of protein production from a repeat expansion appears therefore to be pathognomonic of C9orf 72 ALS/FTD. Whether it is just a biomarker or has a mechanistic role in pathogenesis remains to be seen.

PAPER OF THE YEAR: TIC DISORDERS

Chosen article: ***Current Controversies on the role of Behaviour therapy in Tourette syndrome. Scahill L, Woods D, Himle M et al. Movement Disorders 2013; 28:1179-1183.***

Reviewer: Dr Hugh Rickards, Consultant in Neuropsychiatry, Birmingham and Solihull Mental Health Foundation NHS Trust. Birmingham. Honorary Reader in Neuropsychiatry, Birmingham University.

Tourettes: a renaissance of behavioural therapies?

Behavioural therapies for Tourette syndrome have been around for a long time. Armand Trousseau, who described this condition prior to Gilles de la Tourette himself, recommended a form of training based on a metronome which was, effectively, behavioural (Rickards et al 2010). In the latter part of the 19th Century and for most of the 20th Century, tic disorders were seen from a psychodynamic perspective. When we emerged from this with more biological ideas following Seignot's first successful treatment of tics with haloperidol (Rickards et al 1997), behavioural treatments were seen as threatening progress and, possibly, as dragging us back to a psychological narrative. Behavioural treatments were attempted in the 1970's in the form of massed practice, but did not really catch on. In the last 10 years however, a number of high quality randomised clinical trials have taken place which have shown behavioural treatments to be effective in reducing tics, at least in the short term. (Piacentini et al 2010. Wilhelm et al 2012).

The paper I have chosen reflects the controversies around behaviour therapy and uses evidence to place these therapies on a par with medications for tic disorders. The authors include two of the main researchers in the area (Woods and Piacentini) as well as senior figures from the US Tourette Syndrome Association. Table 1 in the paper directly contrasts the randomised studies of both drug and behavioural therapies. Subject numbers and duration of treatment tends to be longer in the behavioural trials with effect size being comparable but possibly a little lower in this group. Drop-outs were a little lower in the behavioural therapy trials suggesting better toleration.

The authors then go on to debunk what they regard as myths around behavioural therapies, particularly that they only work for mild tics, that they are too much effort, that gains are less durable or that "symptom substitution" occurs.

Finally, they tackle the idea that an effective behavioural therapy would lead to the "recasting of TS as a psychological, rather than a neurological disorder" by refuting this as a false dichotomy. Certainly, the last year has also seen advances in the genetics of the disorder, indicating differences particularly in the genetics of the histamine system (Karagiannidis et al 2013), showing that simultaneous understanding in both the biological and psychological domains is possible and desirable.

The renaissance of behavioural therapies in Tourette syndrome signifies a maturity in the conceptualisation of this disorder which has shifted from "organic" to "functional" and back again in the last 150 years. Finally, we might be shedding this false skin of dualism and moving forward in a more integrated manner.

References:

Support for the histaminergic hypothesis in Tourette syndrome: association of the histamine decarboxylase gene in a large sample of families. Karagiannidis I, Dehning S, Sandor P et al. Journal of Medical Genetics 2013. Jul 3 [Epub ahead of print]

Behaviour therapy for children with Tourette disorder: A randomised controlled trial. Piacentini J, Woods DW, Scahill L et al. JAMA 2010; 303:1929-1937

"Trousseau's disease" a description of the Gilles de la Tourette syndrome 12 years before 1885. Rickards H, Woolf I & Cavanna AE et al. Movement Disorders 2010; 25:2285-2289

Seignot's paper on the treatment of Tourette's syndrome with haloperidol. Rickards H, Hartley N & Robertson MM. Classic Text No.31. History of Psychiatry 1997; 31:433-436

Randomized trial of behaviour therapy for adults with Tourette's disorder. Wilhelm S, Peterson AI, Piacentini J et al. Archives of General Psychiatry 2012; 69:795-803

PAPER OF THE YEAR: EPILEPSY

Chosen article: ***Local cortical dynamics of burst suppression in the anaesthetized brain. Lewis LD, Ching S, Weiner VS et al. Brain 2013; 136: 2727-2737.***

Reviewer: Dr Mark Manford, Consultant neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospitals NHS Trust.

Unravelling burst suppression

Burst suppression of the EEG is an enigmatic state. In the past it has been argued that it is the Holy Grail of treatment in the treatment of status epilepticus. It is also seen in some severe pathological (comatose) states and yet little has been understood about what it is or what it means. Investigating it in animals with small brains provides relatively little opportunity to generate data meaningful for the human condition where cortical distances are much greater.

The authors took five patients who were being investigated for epilepsy surgery with intracranial EEG and made measurements of the burst suppression state, looking at the correlation of discharges across brain regions sampled and their temporal association as well as the time course and spectral frequency of the discharges. They found that burst suppression is not a uniform condition but that bursts sometimes occur in one place and not in others and that the closer to each other were the electrodes, the more likely they were to burst together, but even then not at precisely the same time. They also found that different regions were more or less likely to enter a burst suppression state with a given dose of anaesthetic and that the pattern was most consistent with the local prior metabolic state determining the likelihood of burst suppression. They hypothesise that a low metabolic activity predisposes to EEG suppression with intermittent escapes of the burst as metabolic state recovers slightly.

Their analysis suggests that the bursts represent the previous activity of that region of the brain, prior to the induction of burst suppression and spectral analysis of the bursts may help to determine when the underlying pathophysiological processes are recovering. The role of thalamocortical connections is important in generating this pattern but this study, with only cortical recordings, could not really assess their contributions.

This paper not only casts light on a conceptually difficult area in epilepsy but may also have significance for the treatment of the most refractory of epileptic states if methods for regional and spectral analysis of the burst suppression EEG were to be developed.

PAPER OF THE YEAR: INTRACEREBRAL HAEMORRHAGE

Chosen article: ***Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. Anderson CS, Heeley E, Huang Y et al. INTERACT2 Investigators. The New England Journal of Medicine 2013;368: 2355-65.***

Reviewer: William Rutherford and Rustam Al-Shahi Salman, Division of Clinical Neurosciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh.

ICH: Under Pressure

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) has a worse outcome than ischaemic stroke and hitherto no specific treatment. Neither the haemostatic drug recombinant activated factor VII nor surgical evacuation appear to be effective for acute ICH. Acute blood pressure reduction is implemented only occasionally because of the poor evidence base for it, despite European and North American guidelines generally recommending antihypertensive treatment if systolic blood pressure exceeds 180mmHg.

Therefore, this year's publication of the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT 2) was a milestone in ICH research, because of its findings and its recruitment of 2,839 participants which was the largest sample size of any ICH trial to date. INTERACT2 was an international, multicentre, prospective, randomised, open-treatment, blinded end-point trial. In participants enrolled within six hours of ICH onset and a systolic BP 150-220mmHg, it compared the effects of BP targets of <140mmHg and <180mmHg on the primary outcome of death or major disability (modified Rankin scale 3-6) at 90 days. Allocation concealment was good. There were no baseline imbalances. There did not appear to be any imbalances between the two arms of the trial that could have confounded the findings (in particular, the frequency of ITU admission was similar between the two groups and if anything 'not for resuscitation' orders were more common in the intensive BP target group). Outcome assessment was not only complete (>98%) but also blind to allocated treatment.

INTERACT2 found that a systolic BP target of <140mmHg might be superior to <180mmHg on the primary outcome (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; p=0.06). However, the intensive BP target seemed superior on a secondary, ordinal analysis of the primary outcome (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; p=0.04), which was added to the statistical analysis plan while the trial was ongoing but before the investigators were unblinded to the final dataset. The absolute risk reduction of 3.6% (number needed to treat=28) was in participants' dependence alone, because there was no difference in death between the two groups (see slide number 11 at http://www.interact2.org/wp-content/uploads/2013/05/RCT-session_INTERACT2_London_20131.pptx). There was no difference in major safety events, including neurological deterioration, between the groups indicating that intensive BP lowering, did not cause harm.

The results appear generalisable, although two thirds of participants were recruited in China. In China, urapidil is used for BP reduction, rather than labetalol, GTN, or nicardipine (which tend to be used in Europe and North America), although different drugs seem unlikely to differ in their effect on outcome. Crucially, the Chinese sub-group showed no interaction with treatment effect, and nor did time to randomisation, baseline BP, history of hypertension, or ICH characteristics.

The interpretation of INTERACT2 is challenging. Puritans may argue that the pre-specified primary outcome did not reach statistical significance and that acute BP reduction had small effects and still only seemed superior (risk reduction in death or dependence 3%, 95% CI 0 to 6; p=0.08) in a meta-analysis of the three randomised trials of acute ICH (INTERACT1, INTERACT2, and ATACH1). On the other hand, the secondary analysis is the most appropriate (because BP reduction is likely work across the range of stroke severities, not just at the dichotomy between dependence and independence), had the investigators compared a systolic BP target of <140mmHg to standard practice they might have found a larger effect, and finally BP reduction can be achieved cheaply if HDU/ITU admission is unnecessary and it appears safe in this context.

Overall, INTERACT2 is welcome news for a condition with so few treatment options. Although we are puritanical in our education and thinking we are also pragmatic in our hearts, so on balance we are sufficiently convinced to implement this intervention in our everyday practice. Who knows, ICH may have two acute treatments if the antifibrinolytic drug tranexamic acid proves to be beneficial, so UK neurologists are encouraged to support the ongoing TICH2 trial (www.tich-2.org).

PAPER OF THE YEAR: STROKE

Chosen article: ***Broderick JP, Palesch YY, Demchuk AM et al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. N Engl J Med 2013; 368:893-903***

Reviewer: Prof Keith W Muir, SINAPSE Professor of Clinical Imaging & Consultant Neurologist, Institute of Neuroscience and Psychology, University of Glasgow, Scotland.

IA thrombectomy: Evaluation of innovation

Reperfusing the ischaemic brain is a logical treatment approach, and intravenous thrombolysis with the recombinant tissue plasminogen activator (rtPA) alteplase (our only proven acute treatment) significantly increases the chance of regaining independence. However, IV alteplase recanalises the occluded artery in only around 50-60% of patients, and is least effective in those with the largest clots (and therefore the most severe strokes). Intra-arterial (IA) devices that can disrupt or remove thrombus offer more effective recanalisation.

The Third Interventional Management of Stroke trial (IMS-3) was the latest in a series of academic trials evaluating IA therapy, dating

back to the late 1990s, pursued tenaciously by the stroke team at the University of Cincinnati and their collaborators. IMS-3 randomised acute ischaemic stroke patients to IV thrombolysis alone, or IV rtPA and IA device.

Regulatory systems in both North America and Europe approve devices on the basis that they do what they say - in this case, remove clot from an artery - and do not require evidence of clinical benefit. Despite no randomised controlled trials (RCTs) supporting clinical efficacy, healthcare systems in several countries offered generous reimbursement for IA thrombectomy using approved devices, fuelling a large number of procedures (>7000 per annum in the USA alone). Regrettably, academic rigor was a lower priority than healthy hospital finances, and IMS-3 took almost 6 years to achieve two-thirds of its planned recruitment, ultimately being terminated on grounds of futility – the data review committee concluded that there was no chance of seeing a significant difference between treatment arms - with 656 participants included.

This premature stop for futility was in itself a surprise for IA thrombectomy enthusiasts; a treatment so self-evidently "better" that randomisation was deemed unacceptable or unethical, clearly had an effect size much less than expected. IMS-3 found no difference between treatment arms for primary and secondary end-points, and also any predefined subgroup, despite superior recanalisation rates for IA treatment.

Trials of interventional procedures are always criticised on the grounds that the devices are not state of the art, the operators are inadequately experienced, and patient selection has been poor, and the duration of IMS-3 inevitably meant that older devices and selection techniques predominated (stent-retrievers and CTA angiography being late evolutions during the trial). However, participating centres were all well-organised, motivated and experienced, and IA thrombectomy was done according to best practice at the time. Despite this, the mean onset-to-procedure start time was 249 minutes. For a condition with such steep decline of benefit with longer onset-to-treatment time (as observed in the IV rtPA trials), this means that effect size in a trial will be small: in real life, this sobering figure from some of the best centres worldwide suggests that many procedures are unlikely to benefit patients.

There is a feeling of déjà vu, even for the déjà vu: IMS-3 emphasises once again that RCT level evidence should underpin adoption of new treatments, even more so when procedures are expensive, invasive and require major service reorganisation to deliver. But we have been here before, with EC-IC bypass, carotid endarterectomy, and stenting for both carotids and intracranial vessels, all self-evidently a good idea, all either ineffective or effective only in specific sub-groups after RCTs. IMS-3 has catalysed a large number of academic and commercial trials that will in the years ahead investigate whether there is a role for IA treatment for stroke, and if so for whom. Perhaps stent-retrievers, CTA selection, and earlier and faster intervention will be the key. It has highlighted also that healthcare and regulatory systems may still inadvertently conspire to trigger widespread adoption of innovations without proper evaluation. The contrasting experience of the MR CLEAN trial in the Netherlands, where IA treatment was not permitted except in the context of an RCT, is a salutary one.

BOOK REVIEW

DINGS: a novel

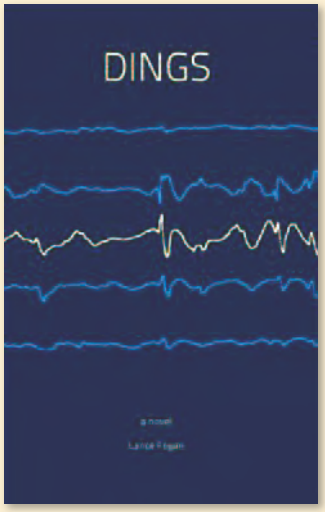
'Dings' is a short novel about epilepsy. Written by retired neurologist, Lance Fogan of Los Angeles, it employs a mother's voice to recount the story of diagnosing temporal lobe epilepsy in her eight-year-old son.

The novel begins with the drama of a nocturnal secondary-generalised attack. There follows an account of its immediate management in the Emergency Department, which includes a lumbar puncture undertaken because the child experiences a somewhat prolonged post-ictal phase, with pyrexia. We then switch back a few months to hear of the child's concentration difficulties at school, misattributed to anxiety at his father being overseas on an army posting. The 'quality item' (of course...) is the final Neurology consultation, wherein a careful history identifies stereotyped episodes of olfactory hallucination and lapses of consciousness (the boy's 'dings') to explain the school difficulties and establish the need for anti-convulsant medication.

'Dings' is well-written and comes nicely bound; it includes a useful glossary. At 259 pages, the length of the main text is just right. Its characterisation is strong – including patient, parents and professionals (at hospital and at school). I read nothing which I would be concerned for a patient or carer to encounter. The mention of Mark Twain's daughter drowning in the bath during a seizure was an interesting tidbit for me; it is not a story that will embellish my own repertoire of epilepsy counsels, however.

Inevitably, there are some American usages and practices, not least the fact the child sees a neurologist rather than a designated paediatric neurologist. These may be slightly distracting for British readers. Presumably, the diagnostic process that is the essence of its plot would be easier to savour if you didn't diagnose epilepsy for a living!

'Dings' may not be great art, or even great science, but it does contain great humanity. It may certainly be recommended to patients as means of reinforcing important points about life with epilepsy, and as means of demystifying this most mysterious of diseases.



Author: Lance Fogan
Published by: Booklocker.com
Price: £14.95
Pages: 259

Reviewed by: Dr Rhys Davies, The Walton Centre NHS Foundation Trust.

Communication Breakdown

Visual Hallucinations in Parkinson's disease as a disorder of attention

Dr James M Shine

BSc (Adv), MBBS, PhD, is the Neuroimaging Research Fellow at the Brain and Mind Research Institute at the University of Sydney, Australia. He is interested in using a combination of fMRI and functional connectivity changes to explain the basic mechanisms underlying brain disorders, with a particular emphasis on attentional breakdowns in Parkinson's disease.

A/Prof Simon JG Lewis

MBBCh, BSc, MRCP, FRACP, MD, is the Director of the Parkinson's Disease Research Clinic at the Brain and Mind Research Institute at the University of Sydney, Australia. He has a long-standing passion for improving the quality of life for patients with Parkinson's disease through the use of novel research programs, spanning cognition, sleep, mood, memory and gait dysfunction. He is also a Consultant Neurologist at Royal Prince Alfred Hospital in Sydney.

Correspondence to:
James Macquarie Shine
BSc MBBS PhD
Neuroimaging Research Fellow
Brain and Mind Research Institute
The University of Sydney
Email: mac.shine@sydney.edu.ac

Simon John Geoffrey Lewis
MBBCh BSc MRCP FRACP MD
Director, Parkinson's Disease Research Clinic
Brain and Mind Research Institute
The University of Sydney
Email: simonl@med.usyd.edu.au

Conflict of interest statement:
The authors state that there are no conflicts of interest.

Provenance and peer review:
Submitted and externally reviewed.

To cite:
Shine JM, Lewis SJG
ACNR2013;V13:6:13-15

Summary

- Visual misperceptions and hallucinations are common in Parkinson's disease and exist along a spectrum.
- Recent work has suggested that visual misperceptions may be related to deficits in attention, rather than pure disorders of perception.
- Results from multimodal neuroimaging studies have provided strong supportive evidence for the hypothesis that visual misperceptions are due to abnormal communication within and between Attentional Control Networks.
- The mechanisms underlying visual misperceptions in Parkinson's disease provide a novel framework for understanding hallcuinatory phenomena in other neurobiological disorders.

Visual misperceptions and hallucinations (VH) occur in over half of all patients with Parkinson's disease (PD), particularly in the latter stages of the condition.[1] These symptoms often occur along a distinct spectrum, with visual misperceptions representing the incorrect recognition of a perceived stimulus and hallucinations representing the occurrence of a perception in the absence of a clear stimulus. Despite their negative impact on patient outcomes,[2] these neuropsychiatric symptoms remain poorly understood in PD, with limited therapeutic options.[1]

Although the pathophysiology of VH is poorly understood, a number of theories have been proposed as explanations for VH in PD. For instance, the presence of VH in clinical disorders that affect the retina, such as Charles Bonnet Syndrome,[3] has led to the proposal that the VH suffered in PD may result from impairments within the visual pathway. In keeping with this hypothesis, it is well recognised in clinical practice that reduced ambient lighting and unfamiliar environments are associated with increased perceptual errors. This has led to the proposal that these visual impairments may induce a partial sensory deprivation that permits the emergence of previously recorded percepts, which then form the basis for VH.[4]

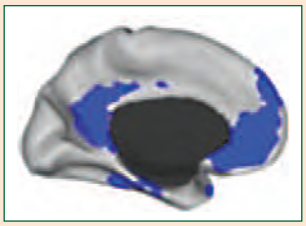
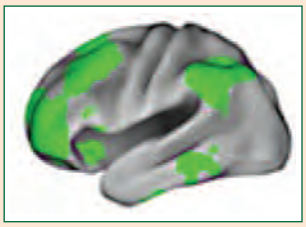
Despite the visual impairments present in hallucinators, it has become increasingly clear these same patients also suffer from specific deficits in executive function and attention. For example, a previous fMRI study has demonstrated that PD patients with chronic VH respond to the presentation of simple visual stimuli with greater frontal and caudate nucleus activation and less visual cortical activation than non-hallucinating PD subjects.[5] In addition, a strong clinicopathological correlation has been found between the presence of VH and Lewy body (LB) pathology within temporal cortical structures, such as the amygdala and parahippocampal gyrus,[6] suggesting that VH in PD relate to a disruption across diverse neural circuitry involved with attention and perception.

These findings have led to several proposals suggesting that hallucinations in PD are related to deficits in perception and attention,[7,8] perhaps due to both modulatory neurotransmitter disturbances as well as specific subcortical and cortical pathology.[6] More recently, combining these insights with findings from the broader neuroimaging literature, it has been proposed that visual misperceptions and hallucinations in PD are due to specific communication breakdowns in the connectivity between the large-scale neuronal networks that subserve attention and conscious perception.

Known as the Attentional Control Networks, these comprise the Dorsal Attention Network (DAN), the Ventral Attention Network (VAN) and Default Mode Network (DMN),[9] each of which is responsible for unique aspects of visual attention (see Table 1). For example, the DAN is consistently activated during tasks that require exogenous attention (e.g. using saccadic eye movements to track an external object), whereas the DMN is more regularly associated with internally focused tasks (e.g. episodic memory recall and internal mentation) (see Table 1). The VAN is presumed to be responsible for the more domain-general function of 'salience monitoring' and also mediates the switch between the DAN and the DMN. Coordinated activity between these networks has been shown to underlie a number of more complex attentional tasks, such as goal-directed episodic recall.[10]

Specifically, the Attentional Networks Hypothesis proposes that VH in PD are due to a relative inability to recruit activation in the DAN in the presence of an ambiguous percept,

Table 1: Attentional control networks, their associated areas and function.
(Adapted from Shine et al. 2011; images from Spreng et al. 2010)

Network	Anatomical Areas	Function
Default Mode Network 	• Medial temporal cortex • Medial prefrontal cortex • Posterior cingulate cortex	• Task-independent introspection • Self-referential tasks
Dorsal Attentional Network 	• Dorsolateral prefrontal cortex • Posterior parietal cortex • Corpus striatum	• Voluntary orienting • Cognitive information processing
Ventral Attentional Network 	• Basolateral amygdala • Lateral and inferior prefrontal cortex • Temporoparietal junction • Ventral striatum	• Mediate activation of other networks • Engages attention to salient stimuli

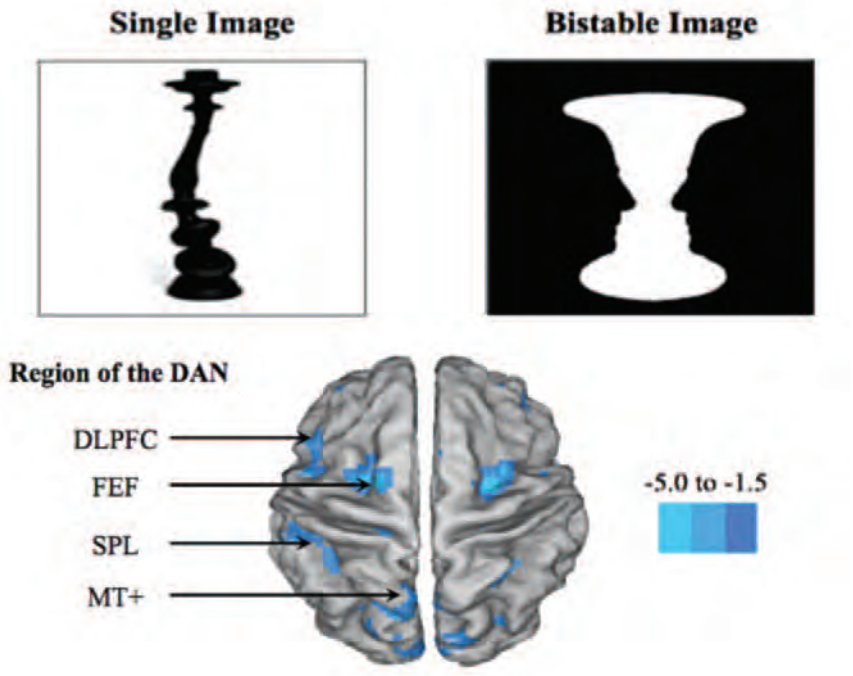


Figure 1 – Functional MRI of the Bistable Percept Paradigm. The top panel shows an example of each image type in the Bistable Percept Paradigm: a Single image, in which there are no hidden elements; and a Bistable image, in which there are two common phenomenological interpretations of the image: a vase and the silhouette of two faces. The bottom panel is a graphical depiction of the brain representing the main regions of decreased BOLD contrast in the comparison of hallucinators when compared to non-hallucinators ($p < 0.001$ and voxels > 10). The major differences were found in regions comprising the Dorsal Attention Network (DAN), such as the dorsolateral prefrontal cortex (DLPFC), the frontal eye fields (FEF), the superior parietal lobule (SPL) and the parietal visual areas (MT+ region). The blue colour intensity in the image reflects the t-statistic from the 2nd level random-effects comparison.

leading to an 'over reliance' on the VAN and DMN. The DAN, which underlies the capacity to focus attention on externally driven percepts, is comprised of widespread neural regions within the frontal eye fields, the dorsolateral prefrontal cortex and the superior posterior parietal cortices, all of which send efferents to the head of the caudate nucleus.[11] The model proposes that an inability to recruit this network would lead to an over-reliance on the VAN and the DMN, both of which are poorly-suited to interpret the content of ambiguous sensory images.[10]

The attentional network hypothesis of VH has received preliminary supportive evidence through behavioural testing using the novel Bistable Percept Paradigm (BPP;[9]). The BPP is a computer-based task that requires participants to evaluate a battery of monochromatic 'monostable' and 'bistable' percepts (see Figure 1) and determine whether there are any images 'hidden' within each picture (e.g. the silhouettes of faces on the edges of the vase in Figure 1). Although the task appears relatively straightforward, performance on the task is able to dissociate patients that hallucinate from those without the symptom. For example, in a cohort of 45 patients with PD, the 23 patients that performed poorly on the BPP were significantly more likely to self-report hallucinations and also displayed specific impairments in attentional set-shifting ability, implicating an inability to effectively recruit the DAN in PD patients with VH.[12]

Impaired performance on the BPP has also been shown to be predictive of specific neuronal impairments in patients with PD. Using Magnetic Resonance Spectroscopy (or MRS), which is a neuroimaging technique that allows for the estimation of neuronal integrity in specific regions of the brain through the exploration of their spectroscopic signature, in a cohort of 22 patients with PD, a recent study found that the severity of impairments on the BPP were associated with reduced neuronal integrity (as measured by the ratio of N-Acetyl Cysteine to Creatine) in the anterior cingulate cortex, a neural hub that connects the DAN and the VAN and is implicated in decision making and conflict monitoring.[13]

In addition to this spectroscopic data, a recent multi-modal neuroimaging study has explored the neural correlates of performance on the BPP in relation to the Attentional Network Hypothesis.[14] In this study, 22 patients with PD performed the BPP in an fMRI scanner while 'on' their regular dopaminergic medications. Hallucinators who had poor performance on the BPP showed significantly decreased activity in their BOLD signal within the DAN in keeping with the major prediction of the Attentional Network model.[14] In addition, structural and resting state data

allowed for the interrogation of grey matter integrity and relative "connectivity" during the brain's "idling" rhythm, respectively. Analysis of the structural brain scans showed that hallucinators had a relative loss of grey matter volume within the anterior insula, a key hub within the VAN that facilitates the shifting of attention to the DAN in the presence of ambiguous visual stimuli. Furthermore, an exploration of the resting state connectivity within the attentional control networks revealed reduced coherence between the DAN and the VAN amongst hallucinators. Together, the findings from these three complimentary analyses were all strongly and predictably inter-related, showing high degrees of inter-correlation, strengthening the notion that each arm of the study was providing insight into a unique aspect of the pathophysiology underlying visual misperceptions and hallucinations.

In conclusion, these results provide support for the notion that VH in PD are due to a breakdown in communication between large-scale neuronal networks that sub-serve attentional mechanisms. Interestingly, the mechanism described above may indeed provide a novel neurobiological framework underlying hallucinations, regardless of the specific disorder in which they occur. For example, extension of these principles to the auditory domain may help explain some of the core features within Schizophrenia with the proposed pathophysiological model operating across similarly disturbed networks. It is hoped that using this novel framework may help to provide the basis for integrated research across disciplines facilitating novel therapeutic strategies. ◆

Visual hallucinations in Parkinson's disease are due to a breakdown in communication between large-scale neuronal networks that sub-serve attentional mechanisms

REFERENCES

1. Diederich NJ, Fenelon G, Stebbins G. & Goetz CG. *Hallucinations in Parkinson disease.* Nature Reviews Neurology 2009;5:331-42.
2. Goetz CG, Fan W, Leurgans S, Bernard B & Stebbins GT. *The malignant course of 'benign hallucinations' in Parkinson disease.* Arch. Neurol. 2006;63:713-16.
3. Ffytche DH. *Visual hallucinations and the Charles Bonnet syndrome.* Curr Psychiatry Rep. 2005;7(3):168:79.
4. Diederich NJ, et al. *Poor visual discrimination and visual hallucinations in Parkinson's disease.* Clin Neuropharmacol 1998;21:289-95.
5. Stebbins GT, et al. *Altered cortical visual processing in PD with hallucinations: an fMRI study.* Neurology 2004;63:1409-16.
6. Harding AJ, Broe GA & Halliday GM. *Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe.* Brain 2002;125:391-403.
7. Collerton D, Perry E & McKeith I. *Why people see things that are not there: A novel Perception and Attention Deficit model for recurrent complex visual hallucinations.* 2005:1-58.
8. Diederich NJ, Goetz CG & Stebbins GT. *Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: Focused review and a new integrative model.* Mov Disord. 2005;20:130-40.
9. Shine JM, Halliday GM, Naismith SL & Lewis SJG. *Visual misperceptions and hallucinations in Parkinson's disease: Dysfunction of attentional control networks?* Mov Disord. 2011;26:2154-9.
10. Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW & Schacter DL. *Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition.* NeuroImage 2010;53:303-17.
11. Asplund CL, Todd JJ, Snyder AP & Marois R. *A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention.* Nature Publishing Group 2010;13:507-12.
12. Shine JM, Halliday GH, Carlos M, Naismith SL & Lewis, SJG. *Investigating visual misperceptions in Parkinson's disease: a novel behavioral paradigm.* Mov Disord. 2012;27:500-5.
13. Lewis SJG, Shine JM, Duffy S, Halliday G & Naismith SL. *Anterior cingulate integrity: Executive and neuropsychiatric features in Parkinson's disease.* Mov Disord. 2012;27:1262-7.
14. Shine JM, et al. *The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease.* Hum Brain Mapp. 2013; EPub Ahead of Print.

Clues to the Causes of Deafness

Professor Karen P Steel, FRS, FMedSci,
is Professor of Sensory Function at King's College London and Honorary Faculty member of the Wellcome Trust Sanger Institute, Hinxton, UK. Her research interests focus on the use of mouse mutants as tools to understand the mechanisms underlying hearing impairment. She has over 200 primary research and review publications and was recently jointly awarded the Grete Lundbeck Foundation's Brain Prize.

Correspondence to:
Wolfson Centre for Age-Related Disorders, King's College London, Guy's Campus, London SE1 1UL, UK
Email: Karen.steel@kcl.ac.uk

Conflict of interest statement:
The work was funded by the Wellcome Trust and MRC. Thanks to Morag Lewis for Figure 2A and Amy Kiernan for Figure 2B. The author declares no conflict of interest.

Provenance and peer review:
Commissioned,
externally peer reviewed

To cite:
Steel KP ACNR2013;V13:6:16-18

Summary:

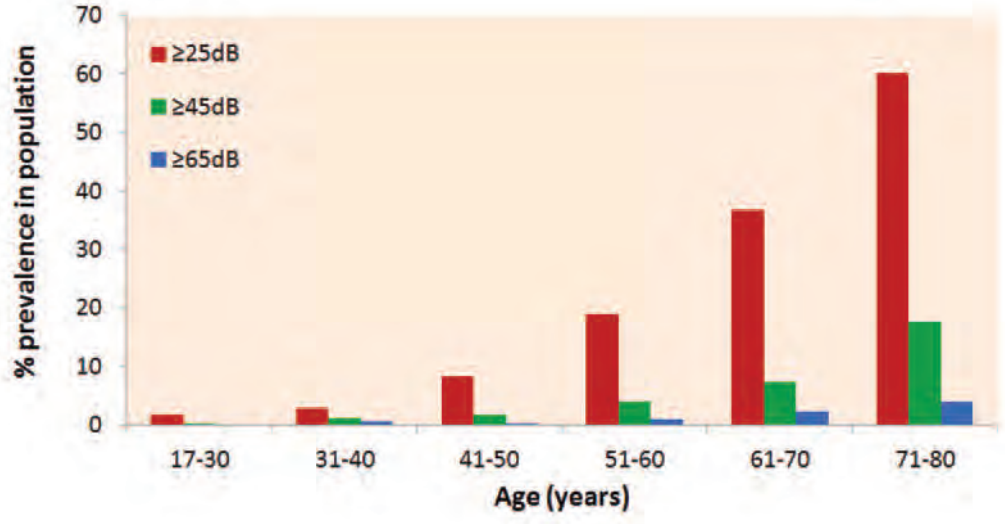
- Hearing impairment is very common and highly heterogeneous.
- Both environmental and genetic factors contribute to deafness.
- Progressive hearing loss is a major target for development of treatments.
- Likely vulnerable sites in progressive hearing loss include: the hair bundle of sensory hair cells; synapses below inner hair cells; and maintenance of cochlear homeostasis by the lateral wall of the cochlear duct.
- Mouse mutants can be used as tools to understand the biological mechanisms and molecular networks underlying human deafness.

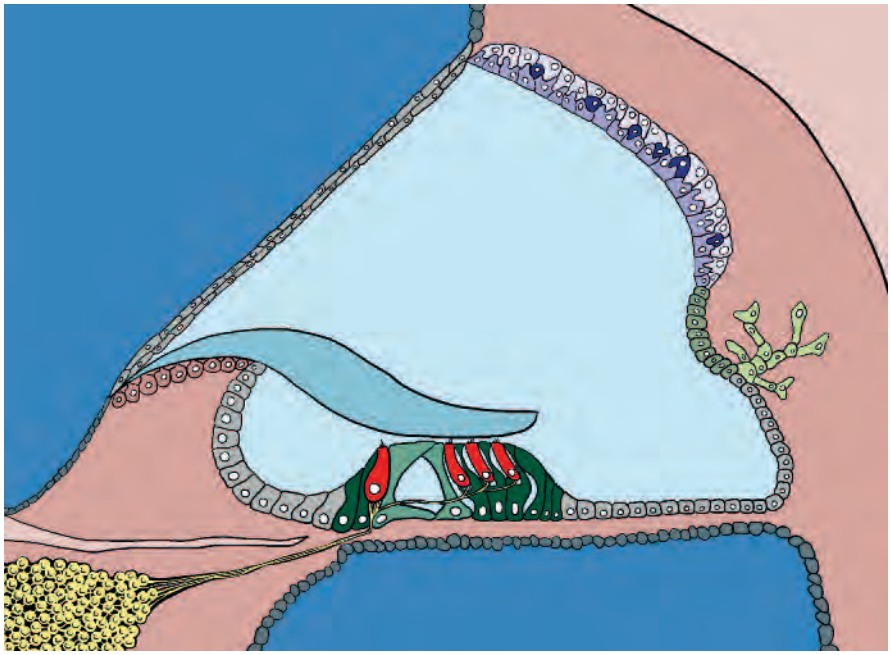
Hearing impairment is the most common sensory disorder in the human population and progressive hearing loss is particularly common. Around 1 in 850 children are born with a significant hearing impairment, and by the end of the first decade of life the number affected is double suggesting a considerable amount of early-onset progressive hearing loss.[1] With each successive decade, more people are affected until over half of adults in the over 70 age group have a hearing loss of 25dB or greater[2] (Figure 1). Despite the clear impact of early developmental defects of the ear on individuals and their families, the majority of people affected by deafness suffer progressive hearing loss, so this is the major problem to be solved. Hearing loss is profoundly isolating, both socially and economically, and has a major impact on the quality of life of those affected. The vast majority of affected individuals have no molecular diagnosis. This is especially true in cases of later-onset, age-related progressive hearing loss.

What do we know about the causes of hearing loss?

Hearing impairment is a heterogeneous disorder with a wide range of causes. We know that noise, drugs, infection and other external factors can trigger hearing loss, but there is a strong genetic component too. It is generally thought that half of all cases of permanent childhood deafness are due to single gene mutations, but this may well be an underestimate. Studies of childhood deafness show that *GJB2* (encoding Connexin 26) is the most frequently associated gene. For example, in the UK, *GJB2* mutations account for one third of cases where there are at least two affected sibs in a family, indicative of a recessive genetic cause.[3] Another recent study of a US patient group (including apparently recessive, dominant and sporadic cases) using massively parallel sequencing of genes known to underlie deafness found 6% of cases were due to *GJB2* mutations.[4] Other genes are involved in much smaller proportions of cases, with the specific genes involved varying between different populations.[3,4] However, cases of childhood deafness with known genetic aetiology represent the minority of cases of hearing impairment (see Figure 1), and there is very little information available on the genetic basis of deafness in the population as a whole. While many people have a single gene mutation causing deafness, others have multiple genes acting together. Other people carry variants of genes which result in an increased susceptibility to damaging agents. The best known example of this is the A1555G mutation of the mitochondrial genome, which confers

Figure 1: The increase in prevalence of different levels of hearing impairment with increasing age. Data from Davis 1995 (ref 2).





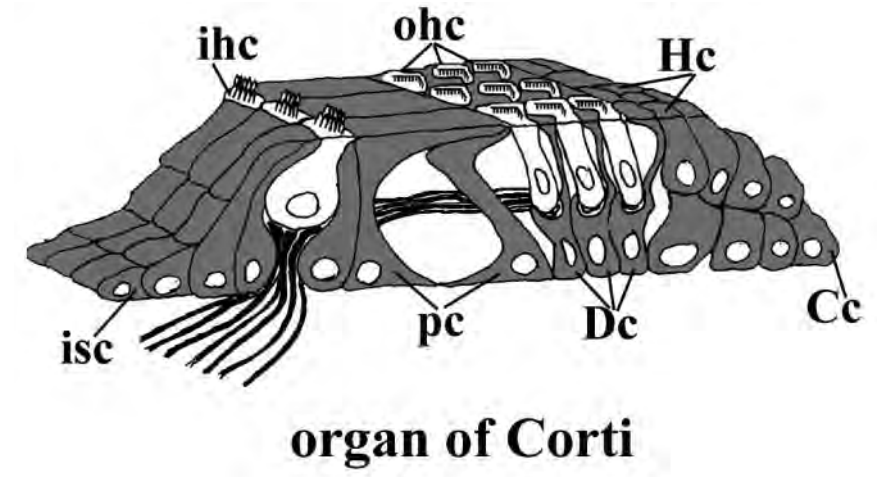


Figure 2A top) Structure of the cochlear duct of mammals. Sensory hair cells (red) are surrounded by supporting cells (green) within the organ of Corti, which sits on the flexible basilar membrane and is deflected during sound delivery. A single row of inner hair cells (left) is innervated by most of the afferent neurons, while three rows of outer hair cells (right) receive mostly efferent innervation (neurons in yellow). The stria vascularis (purple) sits within the lateral wall of the cochlear duct and generates the high potassium level and high resting potential of the endolymph (pale blue) bathing the tops of the hair cells.

Figure 2B bottom) The organ of Corti in detail, showing inner hair cells (ihc), outer hair cells (ohc) and several of the specialised types of supporting cells: pillar cells (pc), Deiters' cells (Dc), Claudius cells (Cc), Hensen's cells (Hc), and inner sulcus cells (isc). Figure 2A was drawn by Morag Lewis, and 2B by Amy Kiernan.

extreme sensitivity to the ototoxic effects of aminoglycoside drugs to carriers,[5] but there will be many further examples where single gene variants or collections of variants in multiple genes (genetic background) influence the susceptibility of a person to hearing loss following an environmental insult. It is difficult to identify these variants directly in humans because of the vast number of differences in the genome amongst individuals, but mice with a uniform genetic background and a mutation affecting a single gene can be used to dissect the underlying molecular basis of deafness. In this respect, genetics, and mouse genetics in particular, can be used as a tool to find genes and proteins associated with hearing ability, and discovery of these genes will be valuable in understanding the molecular processes underlying hearing loss whatever the trigger.

The research community has been remarkably successful in identifying genes underlying childhood deafness, including both syndromic forms and non-syndromic deafness. In the latter case, there are few clues to distinguish different types of hearing impairment. For this reason, gene identification has often relied upon tracking the inheritance of mutations in very large families or population isolates where it is likely that a single mutation is involved. Since the first gene (*GJB2*) involved in non-syndromic deafness was identified in 1997 by Kelsell and colleagues,[6] 65 genes have been discovered with mutations causing uncomplicated hearing impairment and a further 48 chromosomal loci have been reported to harbour mutations leading to non-syndromic deafness. Up-to-date details of these are listed in the Hereditary Hearing Loss website.[7] There are many additional genes associated with syndromic deafness.[8] Thus, there are likely to be several hundred genes implicated in human hearing impairment.

The types of genes involved in deafness are varied, covering a wide range of functions from transcription factors, extracellular matrix proteins, ion channels and transporters, junctional proteins, a range of unconventional myosins and associated scaffolding proteins, and molecules involved in synaptic function.[9] Given the complex and highly specialised nature of the auditory system and its exquisite organisation, able to detect extremely small movements of less than a nanometer presented at rates of up to 100,000 times per second, it is not surprising that many different genes are involved.

Within the cochlea, the organ of Corti contains sensory hair cells that detect the mechanical stimulus of sound through the deflection of the array of stereocilia (modified microvilli) on their upper surface, which in turn puts tension on fine links between adjacent stereocilia directly opening the transduction channel (Figure 2). Cations flood through the open channel and depolarise the hair cell, initiating synaptic activity at the base of the cell. The rapid entry of cations is driven by a strong electrochemical gradient as the stereocilia are bathed by endolymph, an unusual extracellular fluid rich in potassium and maintained at a resting potential of around +100mV, while the internal voltage of the hair cell is around -60mV. Hair cells are surrounded by a set of highly differentiated supporting cells, some of which appear specialised to hold the hair cells rigidly in place while others express genes suggesting a role in homeostasis (Figure 2b). Inner hair cells are the primary receptor cells, receiving most of the afferent innervation. Outer hair cells respond to depolarisation by changing their length, boosting the motion of the organ of Corti and thus acting as amplifiers of the mechanical stimulus delivered to the inner hair cells.

Unlike mechanosensory epithelia in other vertebrates, the adult mammalian organ of Corti is unable to regenerate hair cells, so when a hair cell is damaged and dies, it is never replaced. The inability to regenerate hair cells may be a result of the extreme structural and functional specialisation of the mammalian cochlea. However, hair cell death is rarely if ever the initial cause of hearing impairment; hair cell death is preceded by dysfunction either of the hair cell itself or associated homeostatic processes.

The mechanisms underlying hearing impairment are as varied as the genes involved, and the mouse has played a key role in understanding these mechanisms. Any part of the auditory pathway can be involved from the external ear, through the middle ear and inner ear to the central auditory nuclei, although there are very few examples of deafness caused by primary central problems. One surprise has been the discovery of nearly 50 single genes in which mutations predispose to otitis media in the mouse.[10] However,

the majority of cases of hearing impairment in humans and the majority of single gene mutations causing deafness in the mouse are associated with primary dysfunction of some part of the cochlea. This dysfunction can result from early developmental defects of the inner ear giving congenital or early-onset deafness, or the dysfunction can have a later onset leading to progressive hearing loss. Judging from what we know about mechanisms involved in progressive hearing loss in animal models, there appear to be three main sites within the cochlea that are particularly vulnerable to pathological processes.

Firstly, the precise arrays of stereocilia (hair bundles) at the top of hair cells are often damaged following excessive noise exposure,[11] and many different genes are required for their normal development and function (e.g. *Myo7a*, ref 12; *Cdh23*, ref 13). Stereocilia can be too long or too short, thin, disorganised, misoriented, collapsed, splayed or fused together in different mouse mutants. Given the role of the hair bundles in auditory transduction and the nature of the fine links between them that are essential for function, it would not be surprising if they were readily damaged in progressive hearing loss.

Secondly, synapses below inner hair cells appear to be particularly vulnerable to damage. Levels of noise exposure that were thought to produce only reversible, temporary shifts in auditory thresholds actually lead to permanent damage.[14-16] Afferent fibres with high thresholds and low spontaneous rates are selectively lost, and these are thought to have a role in detecting sounds in noisy backgrounds, a feature that is often an early sign of hearing loss in humans. Furthermore, a common consequence of exposure to damage is swelling of the afferent nerve endings below inner hair cells, a classic indicator of glutamate excitotoxicity, again indicating this is an area of vulnerability.[17-18]

Thirdly, the lateral wall of the cochlear duct (Figure 2a) has a key role in controlling homeostasis of the local environment of the organ of Corti, including pumping potassium into the endolymph at such a rate that its resting potential is maintained at its normal high level of +100mV. This is a highly energy-dependent process, requiring an ample blood supply as found in the stria vascularis on the lateral wall opposite the organ of Corti. Reduced potentials have been reported in some models of progressive hearing loss.[19] Signs of deficient fluid homeostasis have been found in human temporal bone specimens, leading to the proposal of a separate pathological process called strial or metabolic hearing loss in progressive or age-related deafness.[20]

Mouse mutants with each of these types of pathology are available to provide clues to the biological mechanisms and molecular networks involved. Using mouse models allows us to develop a greater understanding of auditory function and pathology which is transferable to humans. Until we have a molecular understanding of the processes underlying progressive hearing loss, it will be difficult to develop treatments. The only remedial options commonly available are hearing aids and cochlear implants, prosthetic devices that provide benefits but do not restore normal function. There is an unmet need for medical approaches to slow down or reverse progressive hearing loss, and the challenge now is to use the new genetic resources available to build that understanding and develop new treatments. ◆

REFERENCES

1. Fortnum HM, Summerfield AQ, Marshall DH, Davis AC, Bamford JM. *Prevalence of permanent childhood hearing impairment in the United Kingdom and implications for universal neonatal hearing screening: questionnaire based ascertainment study.* British Medical Journal 2001;323:536-40.
2. Davis AC (1995) *Hearing in Adults.* London: Whurr.
3. Hutchin T, Coy NN, Conlon H, Telford E, Bromelow K, Blaydon D, Taylor G, Coghill E, Brown S, Trembath R, Liu XZ, Bitner-Glindzicz M, Mueller R. *Assessment of the genetic causes of recessive childhood non-syndromic deafness in the UK – implications for genetic testing.* Clin Genet 2005;68:506-12.
4. Shearer AE, Black-Ziegelbein EA, Hildebrand MS, Eppsteiner RW, Ravi H, Joshi S, Guiffre AC, Sloan CM, Happe S, Howard SD, Novak B, Deluca AP, Taylor KR, Scheetz TE, Braun TA, Casavant TL, Kimberling WJ, Leproust EM, Smith RJ. *Advancing genetic testing for deafness with genomic technology.* J Med Genet. 2013;50:627-34.
5. Prezant TR, Agapian JV, Bohlman MC, Bu X, Öztas S, Qiu WQ, Arnos KS, Cortopassi GA, Jaber L, Rotter JI, Shohat M, Fischel-Ghodsian N. *Mitochondrial ribosomal RNA mutation associated with both antibiotic–induced and non–syndromic deafness.* Nature Genetics 1993;4:289-94.
6. Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, Leigh IM. *Connexin 26 mutations in hereditary non-syndromic sensorineural deafness.* Nature 1997;387:80-3.
7. Van Camp G, Smith RJH. *Hereditary Hearing Loss Homepage.* 2013; URL: http://hereditaryhearingloss.org
8. Online Mendelian Inheritance in Man, OMIM®. 2013; URL: http://omim.org/
9. Dror AA, Avraham KB. *Hearing impairment: a panoply of genes and functions.* Neuron 2010;68:293-308.
10. Tyrer HE, Crompton M, Bhutta MF. *What Have We Learned from Murine Models of Otitis Media?* Curr Allergy Asthma Rep. 2013;PMID:23775349 (in press).
11. Wang Y, Hirose K, Liberman MC. *Dynamics of noise-induced cellular injury and repair in the mouse cochlea.* J Assoc Res Otolaryngol. 2002;3:248-68.
12. Gibson F, Walsh J, Mburu P, Varela A, Brown KA, Antonio M, Beisel KW, Steel KP, Brown SD. *A type VII myosin encoded by the mouse deafness gene shaker-1.* Nature 1995;374:62-4.
13. Di Palma F, Holme RH, Bryda EC, Belyantseva IA, Pellegrino R, Kachar B, Steel KP, Noben-Trauth K. *Mutations in Cdh23, encoding a new type of cadherin, cause stereocilia disorganization in waltzer, the mouse model for Usher syndrome type 1D.* Nat Genet. 2001;27:103-7.
14. Kujawa SG, Liberman MC. *Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth.* J Neurosci. 2006;26:2115-23.
15. Kujawa SG, Liberman MC. *Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss.* J Neurosci. 2009;29:14077-85.
16. Furman AC, Kujawa SG, Liberman MC. *Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates.* J Neurophysiol. 2013;110:577-86.
17. Pujol R, Puel JL, Gervais d'Aldin C, Eybalin M. *Pathophysiology of the glutamatergic synapses in the cochlea.* Acta Otolaryngol. 1993;113:330-4.
18. Robertson D. *Functional significance of dendritic swelling after loud sounds in the guinea pig cochlea.* Hear Res. 1983;9:263-78.
19. Schulte BA, Schmiedt RA. *Lateral wall Na,K-ATPase and endocochlear potentials decline with age in quiet-reared gerbils.* Hear Res 1992;61:35–46.
20. Schuknecht HF, Gacek MR. *Cochlear pathology in presbycusis.* Ann Otol Rhinol Laryngol. 1993;102:1-16.

The Use of Virtual Reality in Assisting Rehabilitation

Madeleine Grealy
is a Professor of Psychology in the School of Psychological Sciences and Health at the University of Strathclyde. Her research interests are in the cognitive rehabilitation following acquired brain injury. With Bilal Nasser she is developing a cybercycle therapy which combines physical exercise and cognitive training. This intervention uses an exercise bicycle adapted for wheelchair users linked to a virtual reality system. She is also interested in age-related changes in perceptuo-motor control and the extent to which perceived movement abilities change the activities older adults engage in.

Bilal Nasser
is a Research Assistant in the School of Psychological Sciences and Health at the University of Strathclyde. He graduated with a BEng Computer and Electronics from Heriot-Watt University and has broad experience in software engineering. He worked with Agilent Technology developing hardware and lab systems, and in Toshiba Medical Visualization on 3D virtual applications. Alongside his research job at the University of Strathclyde, Bilal is doing a PhD and his research interests are in applying Virtual Reality to hand rehabilitation.

Correspondence to:
Professor Madeleine Grealy
School of Psychological Sciences and Health, University of Strathclyde
40 George Street
Glasgow G1 1QE, UK.

Conflict of interest statement:
The authors declare that there are no financial or commercial conflicts of interest.

Provenance and peer review:
Submitted and internally reviewed.

To cite:
Grealey M, Nasser B
ACNR2013;V13;6:19-20

Summary
- Recent technological advances in the computer and games industries have transformed our homes and workplaces and are now making an impact in clinical settings.
- Computer-assisted rehabilitation programmes that make use of Virtual Reality are poised to revolutionise how therapy is delivered, but we still know relatively little about the potential benefits of this form of intervention.
- This review outlines our current knowledge and highlights some of the areas for future research.

Using virtual reality (VR) to assist with rehabilitation is an attractive option for many reasons. With the desire to increase the intensity and frequency of therapy sessions whilst maintaining or cutting costs, the use of VR provides a feasible and efficient method of delivering therapy. VR systems are based on three dimensional computer generated simulations of the real world. Interacting with these simulations creates compelling perceptual illusions which allow the user to behave in the virtual world in a similar way to how they behave in the real world. The capability that this type of interaction affords means that VR systems have many advantages in rehabilitation settings; they can provide safe environments which can be tailored to meet the individual's needs, they can mimic real situations, they can make boring repetitive tasks more engaging and interesting, they enable detailed monitoring of performance to be taken and they allow specific and measureable goals to be set. VR also offers a variety of mechanisms for therapeutic gain including the repetitive practice of movements, engaging in problem solving, memory and attention tasks and exposure to anxiety provoking stimuli or events. Until recently though the use of VR in rehabilitation has been described as 'more virtual than real'[1], but with rapid developments in affordable software and hardware this is changing rapidly. Today the number and nature of computer-based interactive tasks that can be used for rehabilitation is growing, and their use is becoming more commonplace. However, in reviewing the current state of play it is clear that whilst the potential for VR-based therapies is significant we still have some way to go before they are embedded in everyday clinical practice or the home.

VR-based therapies have been used for a variety of conditions including movement disorders, pain management,[2] cognitive deficits[3] and anxiety disorders[4] but the most commonly reported and assessed neurorehabilitation applications have been in postural control[5,6] and stroke rehabilitation. Assessing the efficacy and effectiveness of VR-based therapies is not straightforward though as the literature on the use of VR in stroke rehabilitation exemplifies. A Cochrane review[7] carried out in 2011 that evaluated the effects of virtual reality and interactive video gaming on upper limb, lower limb and global motor function after stroke, revealed only 19 randomised control trials that met the inclusion criteria and 12 of these had sample sizes of less than 25 participants. Whilst the conclusions of this review were favourable for the use of VR and interactive video gaming in improving arm function and activities of daily living in stroke rehabilitation, there was insufficient data to draw more conclusions. This lack of empirical evidence also extends to which aspects of VR-based therapies will be the most important for different groups of patients, and whether the benefits of VR-based therapies are maintained in the long term.

Similarly, a meta-analysis to determine whether VR-based therapies provide additional benefits for arm motor recovery after stroke published in 2011[8] included 12 studies of which only five were randomised control trials. When pooled the data showed that the patients who were randomised to the VR-based therapy were 4.9 times more likely to improve their motor strength compared to patients in the control conditions. However, there were no large studies which compared conventional therapy to VR-based therapy, and a large and varied number of outcome measures were used in the different trials included in this review.

This poor evidence base for the efficacy of VR-based therapies reflects a number of difficulties. The cost of equipment and the need for skilled programmers to create bespoke virtual environments has restricted research programmes in the past, although this is improving. Greater difficulties lie in the designing of informed games-based tasks and in understanding the nature of how the intervention could or should be delivered. Lange et al.[9] described seven core elements that a VR-based intervention should address, including specifying the precise tasks to be targeted for rehabilitation and adjusting the levels of difficulty as the person progresses. This indicates that clinicians and therapists have critical roles to play in designing and implementing VR interventions, and the impor-

tance of this was raised by Levac et al.[10] who pointed out that VR systems are tools whereas VR-based therapies involve making decisions about the appropriateness of the VR system in terms of the person's ability to interact with it, the types of VR tasks to be used, frequency of use, rates of progression etc. The role of the therapist in ensuring the clarity of instructions and objectives, and helping with the initial interactions with the virtual world has been documented in a qualitative study of stroke patient's experiences of VR-based therapy,[11] but unfortunately within the current quantitative literature the processes and procedures surrounding how interventions were delivered are generally not well described.

The rapid evolution of the technology in this field has seen different forms of VR systems come on the market ranging from fully immersive room sized systems to the more common non-immersive experience of using a games console or a computer and monitor. The range of ways in which individuals can interact with virtual environments has also expanded with the invention of haptic and force feedback devices which provide tactile sensations and allow the user to grasp and feel objects in the virtual world. Recent advances in augmented reality (where the user wears a head mounted display and views the real world, but with the addition of computer generated information overlaid onto the scene) may also prove to be useful in rehabilitation settings. Alongside these developments the games industry is also making an impact on rehabilitation with products such as the Nintendo Wii being incorporated into therapies. However, viable concerns are being raised about games that have been designed for entertainment being used in therapeutic settings.[12] Studies that have classified the content of games[13] will certainly help clinicians decide the appropriateness of the game, but knowing whether playing the game will generate the most appropriate movement pattern or behaviour is more challenging. For example, the mapping of a patient's movement amplitude and direction to the movements of an avatar in the game may not be sufficiently sensitive to provide adequate feedback,[13] and when patients have been asked about how they played the games some have admitted to 'cheating' by making proscribed rather than prescribed movement patterns in order to gain more points in the game.[11]

Overall, there is good evidence for the feasibility of using VR-based therapies in neurorehabilitation, although consideration needs to be given to the kinds of devices used since some have the potential to cause cybersickness (nausea, eyestrain, blurred vision etc.).[14] However, robust evidence for the effectiveness and efficacy of this type of therapy is yet to emerge although the signs are promising. Clearly much more work needs to be done and future studies will need to explore not only the functional outcomes of VR-based therapies but also the extent to which they influence cortical reorganisation. Some progress has already been made on this, for example, a preliminary report using fMRI to assess changes in five patients with hemiparetic stroke who had received VR training daily for five weeks indicated that following VR training there was a decrease in the ipsilateral activation and an increase in contralateral activation of the sensorimotor cortex when moving the affected limb.[15] Future work also needs to consider the extent to which there is transfer from the virtual to the real world, and a greater understanding of the mechanisms that promote change in VR-based rehabilitation settings will aid this. These challenges are likely to be met soon since this rapidly developing field has seen the creation of numerous research laboratories and companies in recent years and the formation of an International Society for Virtual Rehabilitation (www.isvr.org). ◆

REFERENCES

1. Crosbie JH, Lennon S, Basford JR, McDonough SM. *Virtual reality in stroke rehabilitation: Still more virtual than real.* Disability and Rehabilitation 2007;29(14):1139-46. DOI: 10.1080/09638280600960909
2. Mahrer NE, Gold JI. *The use of virtual reality for pain control: A review.* Current Pain and Headache Reports 2009;13(2):100-09. DOI: 10.1007/s11916-009-0019-8
3. Cherniack EP. *Not just fun and games: applications of virtual reality in the identification and rehabilitation of cognitive disorders of the elderly.* Disability and rehabilitation. Assistive technology 2011;6(4):283-9. DOI: 10.3109/17483107.2010.542570
4. Opris D, Pintea S, Garcia-Palacios A, Botella C, Szamoskozi S, David D. *Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis.* Depress. Anxiety 2012;29(2):85-93. DOI: 10.1002/da.20910
5. Duque G, Boersma D, Loza-Diaz G, Hassan S, Suarez H, Geisinger D, et al. *Effects of balance training using a virtual-reality system in older fallers.* Clinical Interventions in Aging 2013;8:257-63. DOI: 10.2147/cia.s41453
6. Meldrum D, Glennon A, Herdman S, Murray D, McConn-Walsh R. *Virtual reality rehabilitation of balance: assessment of the usability of the Nintendo Wii() Fit Plus.* Disability and rehabilitation. Assistive technology 2012;7(3):205-10. DOI: 10.3109/17483107.2011.616922
7. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. *Virtual reality for stroke rehabilitation.* Cochrane database of systematic reviews (Online) 2011(9):CD008349-CD49. DOI: 10.1002/14651858.CD008349.pub2
8. Saposnik G, Levin M, Stroke Outcome Res Canada S. *Virtual Reality in Stroke Rehabilitation A Meta-Analysis and Implications for Clinicians.* Stroke 2011;42(5):1380-86. DOI: 10.1161/strokeaha.110.605451
9. Lange B, Koenig S, Chang C-Y, McConnell E, Suma E, Bolas M, et al. *Designing informed game-based rehabilitation tasks leveraging advances in virtual reality.* Disability and Rehabilitation 2012;34(22):1863-70. DOI: 10.3109/09638288.2012.670029
10. Levac DE, Galvin J. *When is virtual reality "therapy"?* Archives of physical medicine and rehabilitation 2013;94(4):795-8. DOI: 10.1016/j.apmr.2012.10.021
11. Lewis GN, Woods C, Rosie JA, McPherson KM. *Virtual reality games for rehabilitation of people with stroke: perspectives from the users.* Disability and rehabilitation. Assistive technology 2011;6(5):453-63. DOI: 10.3109/17483107.2011.574310
12. Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. *Brains on video games.* Nature Reviews Neuroscience 2011;12(12):763-68. DOI: 10.1038/nrn3135
13. Deutsch JE, Brettler A, Smith C, Welsh J, John R, Guarrera-Bowlby P, et al. *Nintendo Wii Sports and Wii Fit Game Analysis, Validation, and Application to Stroke Rehabilitation.* Topics in Stroke Rehabilitation 2011;18(6):701-19. DOI: 10.1310/tsr1806-701
14. Bruck S, Watters PA. *Accessible virtual reality therapy using portable media devices.* Studies in health technology and informatics 2010;154:87-91.
15. Jang SH, You SH, Hallett M, Cho YW, Park C-M, Cho S-H, et al. *Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study.* Archives of Physical Medicine and Rehabilitation 2005;86(11):2218-23. DOI: 10.1016/j.apmr.2005.04.015.

Introduction to the ACNR Stroke Series

Stroke is the commonest neurological condition by some margin, and has been estimated to cause more than 50% of the burden of disease (in terms of quality adjusted life years) of all neurological conditions. It is the third commonest cause of death and leading cause of adult neurological disability. In the last 20 years, stroke has undergone perhaps the most dramatic increase in understanding and treatment (from hyperacute care through to prevention and rehabilitation) of any neurological disease, making it a very exciting time to work in the field.

The aim of this series for ACNR is to capture some of the excitement of recent advances (from endovascular therapy to stroke prevention and rehabilitation) with an eye to future developments including the increasingly important areas of stroke genetics, vascular cognitive impairment and cerebral haemorrhage. However, the series also touches on some of the historical foundations of modern stroke medicine. With the huge breadth of research related to stroke, this series can only hope to provide a highly selective glimpse into a few aspects. Nevertheless, we hope that it will be of interest to both experienced neuroscience clinicians but also to younger clinicians and researchers in the neurosciences: there has never been a more exciting time to start a career in stroke medicine or research.

In the first article in this series, Dafydd Thomas and colleagues provide a fascinating and inspiring account which reminds us of how many fundamental concepts (e.g. that of the ischaemic penumbra, which underpins thrombolysis and endovascular treatments) and technological developments (e.g. computed tomography and magnetic resonance imaging) owe much to the pioneering work done by British researchers, mainly in the latter part of the 20th century.

David Werring, Reader in Clinical Neurology,
UCL Institute of Neurology,
National Hospital for Neurology and Neurosurgery,
Queen Square, WC1N 3BG.

Professor DJ Thomas
Retired Professor of Stroke Medicine at Imperial College and Consultant Neurologist, St Mary's and the National Hospital, Queen Square.

Professor John Marshall
Retired Professor of Neurology, the National Hospital and the Institute of Neurology, Queen Square.

Dr RW Ross Russell
Retired Physician to the National Hospital, Queen Square, St Thomas' Hospital and Moorfields Eye Hospital.

Professor Lindsay Symon
Retired Professor of Neurosurgery, the National Hospital and the Institute of Neurology, Queen Square.

Correspondence to:
Professor Dafydd Thomas,
Box 118, National Hospital for Neurology and Neurosurgery,
Queen Square, London, WC1N 3BG
Tel: 01753 663698
Email: dafydd.thomas@imperial.ac.uk

Conflict of interest statement:
The authors indicate that there are no financial or other conflict of interests.

Provenance and peer review:
Commissioned and externally peer reviewed.

To cite:
Thomas D, Marshall J, Ross Russell RW, Symon L ACNR2013;V13:6:21-25

Foundations of Modern Stroke Medicine:

The British Contribution in the 20th Century

At the end of the 20th Century, not only were we much less likely to suffer a premature stroke than at the start of the Century, but also much more likely to receive an accurate diagnosis and effective treatment. This paper attempts to summarise some of the critical British contributions to the advances in stroke prevention and treatment, but does not pretend to be a comprehensive review.

From being a 'Cinderella disease' where it was felt that little could be done and patients were sometimes left 'languishing' in medical wards, often for months, our main hospitals now have urgent transient ischaemic attack (TIA) clinics, hyperacute stroke units (providing thrombolytic treatment), and active rehabilitation services.

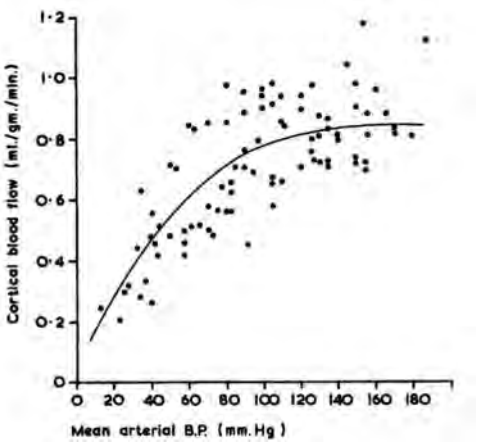


Figure 1: Autoregulation curve (from ref 1), courtesy of Editor of *J Neurol Neurosurg Psychiatry.*

Pathophysiology

A greater understanding of the control of the cerebral circulation in health and disease was achieved using newer techniques for measuring cerebral blood flow (CBF). Murray Harper's[1] work improved awareness of cerebral autoregulation, by which blood flow is kept constant, with changing blood pressures (see Figure 1, which shows a stable CBF throughout a wide BP range). At very high blood pressure, autoregulation begins to fail and CBF rises, increasing the risks of oedema and haemorrhage. The concept developed that blood vessels in the neighbourhood of a stroke were also damaged and lost the ability to autoregulate. Local CBF then became dependent on blood pressure (the pressure-passive response) and vulnerable to both low and high blood pressures.

The Queen Square CBF group (du Boulay, Marshall, Ross Russell and Symon) was set up following the innovative work of Lassen and Ingvar. The group helped emphasise the role of CO2 in controlling CBF and the influence of high blood viscosity and high hamatocrit in lowering CBF.[2] Venesection was shown to have a dramatic effect on increasing CBF even in people with haematocrit levels in the upper normal range.[3] Substantial reductions in risk of occlusive vascular events, including stroke, in patients with polycythaemia was achieved by advising the lowering of the target haematocrit from 0.50 to below 0.45,[4] thereby halving the whole blood viscosity. However, enthusiasm for using haemodilution to improve CBF after stroke in patients without polycythaemia waned in the UK, when the Queen Square CBF Group went on to show that CBF increased largely due to maintaining oxygen delivery rather than due to lowering viscosity.[5] Nevertheless, haemodilution continued to be used for some years elsewhere in Europe and in the USA to increase CBF, reasoning that increasing blood flow to vulnerable areas was beneficial however it was achieved.

The important concept of the ischaemic penumbra, with threatened but still viable cells surrounding a severely ischaemic centre[6] and thresholds in cerebral ischaemia was investigated by Lindsay Symon's group at the Institute of Neurology, Queen Square. This concept underpins the only licensed treatment for acute ischaemic stroke: intravenous thrombolysis. Ischaemic areas lose autoregulation and perfusion can be increased by induced hypertension.[7] The potential damaging effect of low blood pressure in the presence of cerebral vasospasm after subarachnoid haemorrhage and the benefits of improving blood flow and cerebral function by raising blood pressure were advocated by them. The syndrome of critical brain perfusion and the clinical recognition and treatment of borderzone (watershed) infarction of the brain were emphasised.[8]

Pathophysiology

The importance of transient ischaemic attacks (TIAs) as warnings of impending strokes was highlighted by Acheson and Hutchinson's natural history paper;[9] they emphasised that the vertebral arteries were also important and recommended that they should be routinely examined. Initially TIAs were thought to be due to 'vasospasm'. Sir George Pickering was one of the first to doubt this.[10] Attention turned to a haemodynamic insufficiency with short-lived reductions in blood flow to a vulnerable region provoked by a fall in blood pressure. However, the work of Marshall and Kendell showed that lowering blood pressure led to global syncopal symptoms, rather than to the focal ones typical of TIAs.[11]

After Miller Fisher's suggestion that emboli from thrombus in neck vessels might be important, came Ross Russell's observations of repeated emboli moving through the retinal arteries in patients with carotid stenosis.[12] The view that most TIAs were thrombo-embolic in origin was strengthened. Attention then focused on potential sources of cerebral emboli not only from the aorta and other major vessels, especially the carotid bifurcation, but also from the heart. The importance of atrial fibrillation became clearer. The role of paradoxical emboli, especially through the commonly patent foramen ovale (PFO), generated much interest and discussion on the pros and cons of closing the PFO, and the role of transcranial Doppler techniques for detecting ongoing microemboli. The significance of platelets in the growth and embolisation of mural thrombus attracted much interest. The use of antiplatelet therapy in reducing thromboembolism was stimulated.[13]

Ross Russell's work on cerebral microaneurysms[14] in the brains of patients with hypertension, and their potential role in cerebral haemorrhage, was a major contribution: renewed interest has been aroused by the demonstration of microbleeds on blood-sensitive MRI, some of which may be associated with microaneurysms.[15]

Epidemiology

The incidence of stroke fell in developed countries from the mid 20th Century, even before effective treatment became available. A similar decline in myocardial infarcts has also occurred. The reasons for this have not been fully explained. Less cigarette smoking has contributed. A controversial suggestion is that the increased availability of refrigeration, both commercially and domestically, substantially reduced the need for salt as a food preservative. This may have had an effect on reducing the prevalence of high blood pressure, the most important remediable risk factor for stroke. The role of infection in increasing the risks of thrombo-embolism, myocardial infarction and stroke and the widespread use of antibiotics possibly reducing these risks also need to be considered.

The Oxford Community Stroke Project[16] was set up by Charles Warlow in the 1980's and it continues to provide useful information, e.g. the proportion of strokes due to cerebral haemorrhage has fallen substantially.[17] There are, nevertheless, still approximately 150,000 new strokes in the UK each year. Stroke remains a major cause of death and the main cause of ongoing disability. Prevention remains a top priority.

Prevention

Since age is the main risk factor for stroke and since the effects of different risk factors are cumulative, it may be more important to treat the elderly than those in younger age groups. This was not appreciated until recently: up to the 1980's, high blood pressure was often left untreated.

Blood Pressure Treatment

Hypertension used to be considered to be a disease, not just as the upper end of the BP range. It is better regarded as a continuum.[18] The BP level at which treatment is recommended has come down and continues to do so. There have been some excellent blood pressure randomised multicentre trials, including the huge ASCOT study coordinated by Peter Sever's team from St Mary's Hopsital.[19] From advising: 'just bring the blood pressure down', management has matured, with the demonstration that different hypotensive agents may have different benefits and disadvantages at different ages and in different racial groups. In patients following stroke, a raised blood pressure was previously often left untreated. Now there is now a substantial body of evidence of benefit from lowering BP to prevent stroke.[20]

Anticoagulant Treatment

Anticoagulant treatment was effective at preventing thromboses in several clinical situations. So, Marshall, Shaw and Bradford Hill[21] performed a very early trial of anticoagulation in TIAs. The results were inconclusive, possibly as a result of small numbers, but also because the ethics of the time ruled that it was unacceptable for the control group to have a placebo. So their controls were given 1mg of warfarin/day, which was then thought to be ineffective. So it was really a trial of 'normal' warfarin doses, controlled by INR, versus low dose warfarin; some of the control group might thus have had some anti-thrombotic protection.

Antiplatelet Treatment

The role of platelets in TIAs became a concern in the 1960's and 1970's. The UK-TIA Aspirin Trial, at the time the biggest study randomising 3,000 patients failed to show a statistically significant benefit on reducing the risk of stroke in patients presenting with TIAs. This was a stimulus for the introduction of meta-analyses of similar trials.[22] Meta-analysis of the aspirin trials available did show a modest benefit in reducing the risk of stroke and myocardial infarction.[23] Low dose aspirin seemed as effective as high dose and was somewhat less likely to produce side effects. Increased statistical awareness has improved trial design. The development of the Clinical Trials Service Unit in Oxford and the International Centre for Circulatory Health at St Mary's, among others, have allowed the UK to coordinate and to participate in several important vascular trials of other anti-platelet agents and fibrinolysis.

Other Preventative Measures

The use of statins has become widespread.[24] Statins are now introduced at cholesterol levels which would have gone untreated in previous decades.

The harmful effects of poorly controlled blood glucose levels in diabetics are now

better appreciated, with concerns over the risks of larger strokes with higher glucose levels.[25] Extensive studies of diabetes management have been carried out by UK clinicians, involved in the largest cohort studies in the world.

Bickerstaff's monograph[26] on 'Neurological complications of oral contraceptives' highlighted the potential risks of stroke. The OCP formulations have since been improved and many strokes prevented.

The important work of Richard Doll and Richard Peto on the risks of smoking has done much to reduce the prevalence of smoking in Western Countries and to reduce substantially the risks not only of cancers but also of vascular disease and strokes.[27]

Carotid Artery Stenosis

In 1954 a team from St Mary's first reported a carotid artery reconstruction in a successful attempt to prevent TIAs progressing to a stroke.[28] This triggered a widespread enthusiasm for carotid endarterectomy. Physicians' concerns were raised about the number of strokes actually being caused by carotid endarterectomy and the invasive angiography that preceded it. So, in the early 1980's the European Carotid Surgery Trial[29] was started, by Charles Warlow with the same core of collaborators as in the UK TIA Aspirin Trial. In 1991, they reported that in patients with more than 70% stenosis, there was an impressive reduction in the risk of stroke. The results were confirmed by a North American Trial[30] coordinated by British born neurologist, Henry Barnett. In addition to clear evidence of efficacy, we now also have a better idea on patient selection.[31]

These studies triggered two large trials of carotid endarterectomy in asymptomatic patients with tight carotid stenoses: the Stroke Association's and Medical Research Council's Asymptomatic Carotid Surgery Trial, ACST[32] and the North American ACAS trials. These again showed a benefit with a 50% reduction in the risk of stroke, but the absolute risks in asymptomatic patients are low and the perioperative risks are not negligible. This has led to a strange polarisation of management advice. Patients seeing surgeons may be advised to have an endarterectomy because by doing so the risk of stoke is significantly reduced. Those seeing a physician may be advised that the absolute risk is low and that best medical treatment should suffice pending any TIAs. There has also been enthusiasm for using carotid angioplasty and stenting instead of endarterectomy. Questions remain. The trials continue. ACST-2 and ECST-2, both UK-led trials, are now recruiting.

Rapid access TIA Clinics

The realisation that the risks of stroke were highest soon after a TIA and that if surgery were delayed the benefit would be lost has led to a change of attitude and the establishment of urgent TIA clinics around the Country, based on evidence in part from the OXVASC study led by Peter Rothwell. The aim is to see patients and to investigate them promptly including with brain scanning and carotid imaging within 24 hours. Rather than being set-up just where local neurologists or physicians were interested, a TIA service became a priority for NHS managers.

Figure 2: Sir Godfrey Hounsfield, courtesy of Andrew Hounsfield.

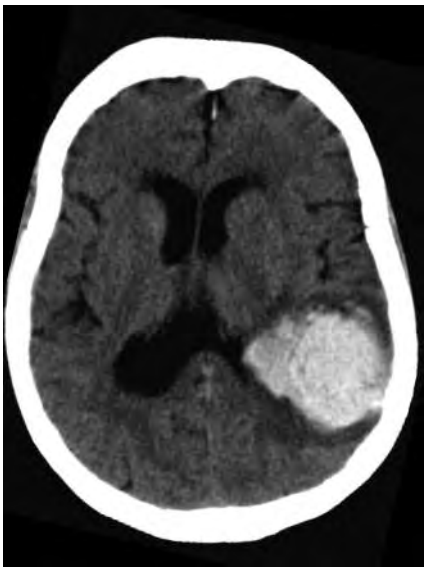


Figure 3: CT scan showing a recent acute lobar cerebral haemorrhage, courtesy of Dr David Werring.

Acute Stroke Diagnosis

Perhaps the greatest contribution to stroke diagnosis and management was the Nobel laureate Sir Godfrey Hounsfield's (see Figure 2), invention of computerised axial tomography.[33] Before the CT scan it was difficult to know whether a stroke was due to an infarct or haemorrhage. Now it is possible to detect significant amounts of acute cerebral haemorrhage within minutes.

As well as permitting anatomical localisation, images of the major arteries are possible and thrombolytic treatment can be given promptly. Thrombolytic treatment had been tried in the late 60's and early 70's, but was abandoned because of fatal haemorrhages – usually in those patients whose stroke had in fact been a haemorrhage, but diagnosed as an infarct (Thomas DJ ,personal observations). See Figure 3 of a CT brain scan showing a recent cerebral haemorrhage, a clear contraindication to thrombolytic therapy.

Diagnosis was further improved by extending the X-ray computerised tomography techniques to nuclear magnetic resonance imaging, for which Sir Peter Mansfield (see Figure 4), also won a Nobel prize.[34] 'Nuclear' was dropped to avoid confusion with ionising radiation. The development of different MR sequences including diffusion-weighted imaging and MR angiography have transformed our assessment and understanding of stroke and have helped improve management. See Figure 5, a diffusion weighted image (DWI) MRI scan showing a recent small subcortical cerebral infarct. An under-emphasised advantage of early brain imaging is that it prevents patients with non-stroke conditions, masquerading as a stroke ("mimics"), receiving inappropriate treatment.

Acute Stroke Treatment

Stroke Units

It came as a surprise that even before any apparently effective treatments became available, patients in units dedicated to stroke care did better than those on general wards.[35] This was not an isolated finding. The reasons are not immediately apparent. Was it just the MDT approach with the concentration of interested medical, nursing and physical therapy staff? Certainly awareness of swallowing difficulties and improved care of the airway helped prevent aspiration problems and undernutrition and dehydration. Hospital trusts became really motivated to provide stroke units only after thrombolytic therapy was accepted to be effective and the number of acute units greatly increased. Many hospitals now have hyperacute units for the first few days with patients moving-on to stroke rehabilitation areas. Lengths of hospital stay have been reduced substantially, and outcomes seem to be improved. The Royal College of Physicians' national sentinel audit for stroke has raised standards and significantly improved stroke care.[36] With a motivated, well-coordinated ambulance service and increased patient and relative awareness, some hospitals are now able to offer thrombolytic treatment to up to 30% of their cases.

Other Acute Treatments

In contrast to the success of thrombolytic treatment,[37] neuroprotective agents have been disappointing.[38] Anticoagulants may have a role (as yet unproven) but only in carefully selected patients.[39] Antiplatelet agents are worth introducing as a secondary prevention after acute stroke to reduce the risk of a recurrent stroke, but the number needed to treat is high.[40] The need to control glucose levels may not be sufficiently addressed. The use of glucose, potassium and insulin infusions were tried again, after a 30 year interval.[25]

Cerebral Haemorrhage

Most of what has been said so far has referred to cerebral infarction. Although some of the same risk factors are involved and rehabilitation may be similar, the acute management of cerebral haemorrhage is quite different. Sir Wylie McKissock, the influential neurosurgeon at Atkinson Morley's Hospital and Queen Square, tested the effect of removing intracranial haematomas in stroke patients. His results were somewhat discouraging.[41] So surgery, with the exception of that for acute cerebellar haemorrhages was largely abandoned in the UK until David Mendelow and his colleagues re-addressed the question. With better modern anaesthetic and post-operative care and less invasive surgery, a multicentre trial was set-up (STICH). Again the results have been discouraging, failing to show overall benefit from surgical evacuation.[42] However, trials of acute blood pressure lowering in cerebral haemorrhage have been promising, and a large UK-led trial of tranexamic acid is underway.

Subarachnoid Haemorrhage

There have been significant advances with fewer open operations, more endovascular procedures and better measures to recognise and control the effects of cerebral vasospasm and maintain cerebral blood flow. Calcium antagonists have been used.[43] Treatment of hydrocephalus has been improved.[44]

Rehabilitation

Rehabilitation results are improved after good acute care, which has minimised the volume of brain damage and has prevented pressure sores, venous thromboses, shoulder subluxation and contractures which all make therapy more difficult.

Therapy can begin in the acute unit, particularly with correct positioning, swallowing assessments, protection of the airway and maintaining nutrition. A goal-orientated approach with a skilled MDT is now widely recommended. The days of not emphasising speech therapy because it was little better than 'just talking to the patient' and not offering a place in rehabilitation to those with marked proprioceptive problems or even a field defect with inattention are happily past. Modern MRI with functional imaging may help with prognosis, predicting and planning brain recovery. The need to recognise those with dementia and other cognitive problems is now better appreciated when rehabilitation is being considered. A substantial number of patients suffer post-stroke depression. This needs to be recognised. It is often amenable to treatment, improving quality of life and motivation.[45]

The Future

The Royal College of Physicians (36) has had an important role in improving stroke services around the UK; the college stroke audit highlighted deficiencies, and managers were motivated to rectify them. The monitoring looks likely to continue. There is no place for complacency. The Stroke Association's survey of patients and carers found that a major criticism was that they felt abandoned on returning home from hospital. There was a sudden lack of medical and nursing care and a dramatic drop in therapy. This separation of hospital and community services needs to be addressed. This problem is not confined to the United Kingdom. In addition, it is disappointing that health and social services remain separated in the UK.

The NHS provides a unique opportunity for translational research, stimulating the creation of the National Institute for Health Research (NIHR) and Stroke Research Network, which has dramatically increased participation of stroke patients in research studies (from about 2,000 per year in 2005 to over 12,000 per year in 2012), which should continue to have have far-reaching beneficial effects.

In the UK, neurologists have been slower to take on the management of the hyper-acute stroke units in the same way as their European and North American colleagues. Hopefully this will be rectified by improvements in the UK training programmes to allow stroke (and all of the acute neurological conditions that can mimic it) to play the central role it deserves in the training of UK neurologists, thus stimulating continued advances in this exciting field. ◆

Figure 4: Sir Peter Mansfield. Courtesy of The University of Nottingham.

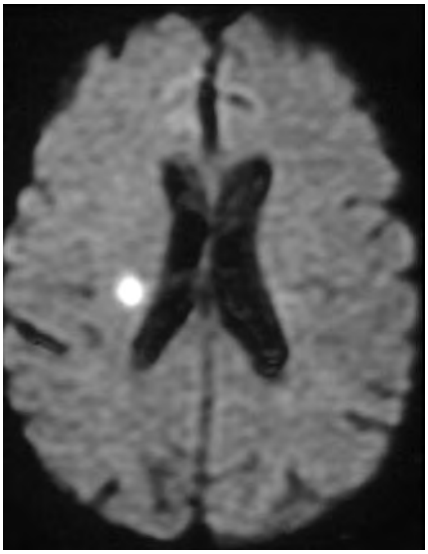


Figure 5.MRI, diffusion-weighted image showing a recent small, subcortical cerebral infarct (bright area),courtesy of Dr David Werring.

REFERENCES

1. Harper AM. *Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex.* J Neurol Neurosurg Psychiat 1966;29:398-403.
2. Thomas DJ, du Boulay GH, Marshall J, Pearson TC, Ross Russell RW, Symon L, Wetherley-Mein G, Zilkha E. *Cerebral blood-flow in polycythaemia.* Lancet 1977;2:161-3.
3. Thomas DJ, du Boulay GH, Marshall J, Pearson TC, Ross Russell RW, Symon L, Wetherley-Mein G, Zilkha E. *Effect of haematocrit on cerebral blood-flow in man.* Lancet 1977;2:941-3.
4. Pearson TC, Wetherley-Mein G. *Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia.* Lancet 1978;2:1219-22.
5. Wade JP. *Transport of oxygen to the brain in patients with elevated haematocrit values before and after venesection.* Brain;106:513-23.
6. Astrup J, Siesjo BK, Symon L. *Thresholds in cerebral ischaemia-the ischaemic penumbra.* Stroke 1981;12:723-5.
7. Symon L, Branston NM, Strong AJ. *Autoregulation in acute focal ischaemia. An experimental study.* Stroke 1976;7:547-54.
8. Ross Russell RW, Page NGR. *Critical perfusion of the brain and retina.* Brain 1983;106:419-34.
9. Acheson J, Hutchinson EC. *The natural history of 'focal cerebral vascular disease'.* Q J Med 1971;40:15-23.
10. Pickering GW. *Transient cerebral paralysis with hypertension and with cerebral embolism.* J Amer.med Ass 1948;137:423-30.
11. Kendell RE, Marshall J. *Role of hypotension in the genesis of transient focal cerebral ischaemic attacks.* Brit med J 1963;2:344-8.
12. Ross Russell RW. *Observations on the retinal blood-vessels in monocular blindness.* Lancet 1961;2:1422-8.
13. Harrison MJG, Marshall J, Meadows JC, Ross Russell RW. *Effect of aspirin in amaurosis fugax.* Lancet 1971;2:743-4.
14. Ross Russell RW. *Observations on intracranial aneurysms.* Brain 1963;86:425-42.
15. Charidimou A, Kakar P, Fox Z, Werring DJ. *Cerebral microbleeds and recurrent stroke risk.* Stroke 2013;44:995-1001.
16. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. *Long-term survival after first ever stroke;the Oxfordshire Community Stroke Project.* Stroke 1993;24:796-800.
17. Lovelock CE, Molyneux AJ, Rothwell PM. *Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK beteen 1981 and 2006 a population-based study.* Lancet Neurol 2007;6:487-93.
18. Pickering GW. *Normotension and hypertension:the mysterious viability of the false.* Am J Med 1978;65:561.
19. Dahlof B, Sever PS, Poulter NR, et al for the ASCOT investigators. *Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethazide as required in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm(ASCOT-BPLA): a multicentre randomised controlled trial.* Lancet 2005;366:895-906.

20. Rashid P, Leonardi-Bee J, Bath P. *Blood pressure reduction and secondary prevention of stroke and other vascular events:a systematic review.* Stroke 2003;34:2741-8.
21. Hill AB, Marshall J, Shaw DA. *A controlled trial of long-term anticoagulant therapy in cerebrovascular disease.* Quart J Med 1960;29:597-609.
22. Peto R, Collins R, Gray R. *Large-scale randomised evidence: large, simple trials and overviews of trials.* J clin Epidemiol 1995;48:23-40.
23. Antiplatelet Trialists' Collaboration. *Secondary prevention collaborative overview of randomised trials of antiplatelet therapy. I.Prevention of death,myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients.* Br Med J 1994;308:81-106.
24. Cholesterol Treatment Trialists' Collaborators (CTT). *Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 09,056 participants in 14 randomised trials of statins.* Lancet 2005;366:1267-78.
25. Scott JF, Robinson GM, French JM, O'connell JE, Alberti KGMM, Gray CS. *Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycaemia.* Stroke 1999;30:793-9.
26. Bickerstaff ER. *Neurological complications of oral contraceptives.* Oxford University Press 1975.
27. Peto R. *Smoking and death: the past 40 years and the next 40.* Br Med J 1994;309:937-9.
28. Eastcott HHG, Pickering GW, Robb CG. *Reconstruction of the internal carotid artery in a patient with intermittent attacks of hemiplegia.* Lancet 1954;2:994-6.
29. European Carotid Surgery Trialists' Collaborative Group. *MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis.* Lancet 1991;337:1235-43.
30. North American Symptomatic Carotid Surgery Trial Collaborators. *Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis.* N Eng J Med 1991;325:445-53.
31. Rothwell P, Warlow CP on behalf of the European Carotid Surgery Trialists' Collaborative Group. *Prediction of benefit from carotid endarterectomy in individual patients.* Lancet 1999;353:2105-10.
32. MRC Asymptomatic Carotid Surgery Trial Collaborative Group. *Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms:randomised controlled trial.* Lancet 2004;363:1491-502.
33. Hounsfield GN. *Computerised transverse axial scanning(tomography):1.Description of system.* Br J Radiol 1973;46:1016-22.
34. Mansfield P, Maudsley AA. *Medical imaging by NMR.* Br J Radiol 1977;50:188-94.
35. Langhorne P, Williams BO, Gilchrist W, Howie K. *Do stroke units save lives?* Lancet 1993;342;395-8.
36. Rudd AG, Irwin P, Rutledge Z et al. *The national sentinel audit for stroke:a tool for raising standards of care.* J R Coll Physicians 1999;33:460-4.
37. Wardlaw JM, Warlow CP, Counsell C. *Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke.* Lancet 1997;350:607-14.
38. Dorman PJ, Counsell CE, Sandercock PAG. *Recently developed neuroprotective therapies for acute stroke.* CNS Drugs 1996;5:457-74.
39. Sandercock P, Mielke O, Liu M et al. *Anticoagulants for preventing recurrence following presumed non-cardio-embolic ischaemic stroke or transient ischaemic attack.* Cochrane Database Syst Rev 2003;1:CD000248.
40. Chen ZM, Sandercock P, Pan HC et al. *On behalf of the CAST & IST collaborative groups.Indications for aspirin use in acute ischaemic stroke:a combined analysis of 40,000 randomised patients from the Chinese Acute Stroke Trial and the International Stroke Trial.* Stroke 2000;31:1240-9.
41. McKissock W, Richardson A, Taylor J. *Primary intracerebral haemorrhage:a controlled trial of surgical and conservative therapy in 180 selected cases.* Lancet 1961;2:221-6.
42. Mendelow AD, Gregson BA, Fernandes HM et al. *Early surgery versus initial conservative treatment in patients with spontaneous supra-tentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage(STICH):a randomised trial.* Lancet 2005;365:387-97.
43. Pickard JD, Murray GD, Illingworth R, et al. *Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial.* Br Med J 1989;298:636-42.
44. Pickard JD. *Early post-haemorrhagic hydrocephalus.* Br Med J 1984;289:569-70.
45. House A, Dennis M, Hawton K, Warlow CP. *Methods of identifying mood disorders in stroke patients:experience in the Oxfordshire Community Stroke Project.* Age Ageing 1989;18:371-9.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th December, 2013

November

Improving Patient Pathways in Parkinson's Disease meeting
5 November, 2013; Newcastle, UK
Supported by Genus Pharmaceuticals.
Register for free at www.parkinsons-ha.co.uk
or www.apo-go.co.uk/hcp/events/PRM-2013

Nurses' Training Day: Chiari Malformation and Syringomyelia
Thursday 7th November 2013
7 November, 2013; Sheffield, UK
T. 01964 535 448 or 07976 400 881,
E. info@britishsyringomyelia-chiarisociety.org

9th ESSENTIAL NEURO MRI Course
Sat 9 Nov, 2013: Liverpool, UK
T. 07799 723 925
E. essentialcourses@hotmail.com

12th Clinical Trials in CNS
18 & 19 November, 2013; London, UK
See www.clinicaltrialscns.com or
T. Jonathan Collins, 020 7827 6734,
E. jcollins@smi-online.co.uk
** Quote SMI2G5N during checkout to receive £300 discount **

Improving Patient Pathways in Parkinson's Disease meeting
21 November, 2013; Birmingham, UK
Supported by Genus Pharmaceuticals.
Register for free at www.parkinsons-ha.co.uk
or www.apo-go.co.uk/hcp/events/PRM-2013

The United Kingdom Acquired Brain Injury Forum 5th Annual Conference
21 November, 2013; London, UK
T. 0845 6080788
E. info@ukabif.org.uk
www.ukabif.org.uk

Developments in the management of hemiplegia
21 November, 2013; Edinburgh, UK
www.hemihelp.org.uk/professionals/conferences

West of England Seminars in Advanced Neurology (WESAN)
21-22 November, 2013; Exeter, UK
Programme and booking online at
www.aquaconferencemanagement.co.uk/wesan/2013-programme
E. barbara@aquavenuesolutions.com

RAatE 2013
25 November, 2013; Coventry, UK
www.raate.org.uk

Speech Disorders Throughout the Lifespan
UCL CDCN Workshop: 26 November, 2013: London UK
E. cdcn@ucl.ac.uk
www.ucl.ac.uk/cdcn/events/forthcomingworkshops

MS Masterclass 2013
28-29 November, 2013; Bristol, UK
Information from Professor Neil Scolding,
E. N.J.Scolding@bristol.ac.uk

December

The Encephalitis Society Professional Seminar
2 December, 2013; London, UK
Free entry for our Professional Members,
for more information
E. admin@encephalitis.info
T. 01653 692585.

Multiple Sclerosis 2013
2 December, 2013; London, UK
Call Jackie on 020 7501 6762,
www.mahealthcareevents.co.uk

UK Stroke Forum
3-5th December, Harrogate, UK
www.ukstrokeforum.org

24th International Symposium on ALS/MND
6-8 December, Atahotel Quark Milan, Italy
E. symposium@mndassociation.org
T. 01604 250505

BNPA December Teaching weekend
13-15 December, 2013: Oxford, UK
T. 020 8878 0573,
E. admin@bnpa.org.uk or
jashmenall@yahoo.com

2014

February

Dementias 2014
13-14 February, 2014; London, UK
Call Jackie on 020 7501 6762,
www.mahealthcareevents.co.uk

2nd UK MSA research meeting: MSA research and clinical interest
27 February, 2014; London, UK
www.eventbrite.co.uk/event/7963026627/eorg

BNPA 27th Annual General Meeting
27-28 February, 2014; London, UK
Register at www.bnpa.org.uk or
T. 0560 348 3951,
E. admin@bnpa.org.uk or
jashmenall@yahoo.com

March

Edinburgh Sleep Medicine Course
17-21 March, 2014; Edinburgh, UK
http://sleep.scot.nhs.uk/education.html/

NEUROLOGY 2014: Leading edge neurology for the practising clinician
27-28 March, 2014; London, UK
www.ucl.ac.uk/ion/education/courses/other/neurology or
E. Jean Reynolds, jean.reynolds@ucl.ac.uk
T. 020 344 84460

Edinburgh Sleep Medicine Course
17-21 March, 2014; Edinburgh, UK
http://sleep.scot.nhs.uk/education.html/

International Brain Injury Symposium:
'How to navigate through the rehabilitation pathway' (Day 1)
'Changes and challenges in Disorders of Consciousness' (Day 2)
March 27 – 28, 2014; London, UK
E. institute@rhn.org.uk
www.rhn.org.uk/bisymposium

April

Optogenetics: controlling the brain with light
3 April, 2014; Oxford, UK
http://www.pharm.ox.ac.uk/

8th World Congress of Neurorehabilitation (WCNR 2014)
8-12 April, 2014; Istanbul, Turkey
For more information see www.wcnr2014.org
or E. traceymole@wfnr.co.uk

Astrocytes in Health and Neurodegenerative Disease
28-29th April, 2014; London, UK
E. conferences@biochemistry.org

May

ABN Annual Meeting
7-9 May, 2014; Cardiff, UK
E. info@theabn.org
T. 020 7405 4060

July

ISMRM Workshop on: Function MRI: Emerging Techniques & New Interpretations
July, 2014; Charleston, SC, USA
www.ISMRM.org
T. +1 510 841 1899

September

ABN Autumn Meeting
30 September-1 November, 2014; Stratford, UK
E. info@theabn.org
T. 020 7405 4060

ILAE British Chapter Medical Students / FY1 Epilepsy Teaching Weekend

Conference details: 13-14 July 2013, Birmingham, UK. ***Report by:*** Sophie Binks, Brighton & Sussex University Hospitals NHS Trust, F1 doctor (academic neurology foundation programme).

Nearly 70 medical students, junior doctors and researchers gathered at the University of Birmingham on a sunny weekend in July to attend a comprehensive programme of epilepsy teaching delivered by experts in the field from the International League Against Epilepsy British Chapter (ILAE). This free event (a £60 booking deposit was refunded on attendance) featured both refreshers on basic epilepsy knowledge as well as more advanced sessions, such as teaching on EEG, neurosurgical interventions and numerous examples of video telemetry – topics which may not be covered in detail in medical school curricula.

The event opened with a welcome from consultant neuropsychiatrist Dr Manny Bagarry, who set the scene with epilepsy definitions and epidemiology. Some thought-provoking facts included that epilepsy is three times more common in resource-poor countries, with a main potentially preventable cause of neurocysticercosis. Next, neuroscientist Professor John Jefferys updated the group on developments in basic science of epilepsy, explaining the different experimental models – human, animal and computational – and exploring how our understanding of ictal behaviour of neural networks is changing. Delegates were left with the impression of an evolving scientific field where new discoveries await to be made. The final plenary session before lunch was from Consultant Neurologist Dr Doug McCorry who revised the causes and differential diagnoses of epilepsy, and revealed he was inspired to choose this sub-speciality due to weight of patient need.

During the first part of the afternoon attendees rotated through different small groups covering history and examination, EEG and neurosurgical work-up and seizure semiology, featuring an invaluable chance to view video telemetry of seizures including focal-onset events and non-epileptic attack disorder. For many of us, the most impactful session of the small group work was a session on sudden unexpected death in epilepsy (SUDEP), facilitated by Nurse Consultant Ms Lynn Greenhill, who introduced the testimony of a couple who had lost their daughter, aged only in her 20s, to this devastating complication. A powerful comparison was drawn between providing information on SUDEP and on prognosis in other serious conditions, such as cancer. Moreover, their story emphasised the value of continuity of care and of appropriate specialist referral in the management of young people with epilepsy.

We then returned to plenary sessions. Dr Doug McCorry presented a review of pharmacotherapy, tracing its origins from phenobarbitol in 1912 – which we learnt is still used in the developing world – to more recent options. Case studies helped with learning of practical points (useful for F1s and final year students about to start work) around efficacy, drug interactions and multi-drug regimens. Consultant Neurosurgeon Mr Ramesh Chelvarajah then closed the day with a thorough overview of all the surgical treatment options available, including 'palliative' procedures of Deep Brain Stimulation and Vagal Nerve Stimulation. As not all junior doctors or students work in centres where such surgery is performed, this was a good opportunity to understand the spectrum of what is offered and steps in pre-surgical evaluation to be able to counsel patients considering surgical intervention.

Plenary sessions on day 2 had a clinical focus with a multi-disciplinary discussion of a complex case study and talks on women with epilepsy (WWE) and children. Ms Greenhill's talk on WWE covered all the salient points of pre-conception, management of drug regimens in the expectant mother and post-partum breast feeding and safety advice. In particular, her talk helped develop prescribing skills through explanation of a number of difficult or controversial areas. Professor Raj Gupta's session on children was notable for an excellent exposition of differentials and syndromic epilepsies combined with plentiful use of video telemetry to demonstrate teaching points. The course ended with delegate prize presentations and a telemetry quiz – a final opportunity to test semiology skills.

This course can be thoroughly recommended to medical students and junior doctors with an interest in neurology, neurosurgery or neuropsychiatry. Not only is it free, but individual en-suite accommodation of a high standard was provided by the ILAE as well as catering including a three-course meal on the first evening, when we had a chance to meet faculty and like-minded medical students and peers. Tuition was superb and enthusiastic throughout, with a chance to ask many questions and (attending as a final year medical student at the time) I felt I learnt something new in every session, despite what could have been a tricky balance to meet the needs of pre-clinical and clinical years students as well as F1s. F1 in academic neurology from Newcastle Dr David Bargiela agreed, saying: "This was a fantastic course, it was especially valuable in introducing the clinical approach to epilepsy diagnosis using video telemetry and EEG. These aspects are rarely covered at medical school or foundation training but the basic introductions provided served well to whet the appetite of those hoping to pursue specialist training in neurology."

Juliet Solomon of ILAE British Chapter commented: "We are really delighted with the positive response to the weekend – it is only the second time we have hosted the course. Feedback received suggests that the weekend was a real success. The atmosphere was great, with lots of interaction. Delegates seemed to have really benefited. Therefore, we hope not only to repeat this event, but based on demand and in collaboration with some of the attendees are also looking to develop a new, clinically-focused course targeted at foundation doctors (F1s & 2s) in the near future!" ◆

For more information please contact Juliet Solomon, Administrative Director, ILAE UK British Chapter on members@ilae-uk.org.uk

The PSP Association International Medical Workshop – 50 years on

Conference details: 25 July 2013, London UK. ***Report by:*** Dr Timothy Rittman is a Clinical Research Fellow in the Department ofClinical Neurosciences at the University of Cambridge, and Dr Sian Alexander, Academic Clinical Fellow in the Department of Clinical Neurosciences at the University of Cambridge.

This year's Progressive Supranuclear Palsy (PSP) Association Meeting marks 50 years from the first description of Richardson's syndrome or PSP as we now know it. The meeting covered PSP and its cousin Corticobasal Degeneration (CBD).

At the end of the day we were left encouraged by recent progress. There was a hint of disappointment that two big trials in PSP have failed to show any impact on disease progression. However, this field has motivated scientists, clinicians and, most importantly, motivated patients. Momentum is building towards improved treatments and care in PSP, in part thanks to a newly formed national network of centres in the UK studying PSP and CBD, well supported by the PSP Association.

Headlines from each session are presented below. The range of talks and breadth of research was impressive, and the cast was stellar in terms of reputation and quality.

The first session covered molecular and genetic aspects of disease. Michel Goedert is firmly of the opinion that the tau protein is responsible for the diseases of PSP and CBD, rather than being a bystander. He presented evidence that tau protein travels from cell to cell through the brain causing mischief. John Hardy followed with an update on the genetics of the tau protein and Genome Wide Association studies in PSP. Results so far point to three processes where damage occurs: integrity of synapses, the myelin sheath and cellular stress response. An intriguing talk from Steve Gentleman discussed another tauopathy, dementia pugilistica. Although the link between head injury and PSP/CBD is far from certain, and dementia pugilistica is quite different from either disease, there are pathological similarities.

Human disease biology came before lunch covering lumbar puncture, imaging techniques and pathology. At the moment these tests are research tools and add little to clinical diagnosis, but there is evidence that they may be relevant to tracking disease progression over time. A tau ligand for PET is a promising new tool, and further work to evaluate its clinical and research utility is eagerly awaited.

The most eagerly anticipated session came just after lunch, in a discussion of therapeutics. David Burn described outcomes of recent trials using sodium valproate and Tideglusib, both targeting tau phosophorylation by inhibiting Glycogen-synthase kinase-3 (GSK-3). Unfortunately, both trials had disappointing outcomes, although for different reasons. In the study of sodium valproate, significant difficulties with safe and accurate drug dosing compromised data validity, demonstrating the difficulty of accurately titrating even well-established drugs with known toxicology. Tideglusib initially emerged as pharmacological target for Alzheimer's disease. However, there is a good case for investigating whether GSK-3 inhibition may be used therapeutically in disorders of hyperphophorylated tau accumulation, such as PSP, CBD and tau variants of FTD. Tideglusib treatment was associated with a small decrease in rate of atrophy in PSP patients compared with matched controls, although not in areas associated with tau accumulation and without associated clinical benefit. Concerns about the potential for widespread on-target side effects from Tideglusib in view of the enzyme's pleiotropy did not emerge. Whether this reflects lack of in vivo bioefficacy may warrant further study, in an effort to determine whether there is a future in further exploring therapeutic modulation of GSK3 inhibitors.

Hugh Nutall (from Eli Lily) had the trickiest talk of the day, trying to predict where PSP/CBD therapies will be in five years' time. He talked about a number of promising compounds in development, some GSK-3 inhibitors and others targeting the tau protein pathway but in a different manner to previous efforts.

In the area of clinical trials, two strikingly positive features emerge. First, the utility and value of the PSP rating scale. Developed by Larry Golbe in 2007, it is being widely used in practice and in trials, enabling better assessment of how individuals with PSP respond to trial medicines. Second, the collegial and collaborative network of PSP researchers was praised by several researchers. This bodes well for ongoing PSP and CBD research.

The final session started with talks covering some good old-fashioned clinical questions of diagnosis and syndromes. Jon Rohrer gave a talk on frontotemporal dementia and tauopathies in a general sense, which brought into sharp focus the importance of collaborative efforts in the study of biologically similar, sometimes overlapping diseases. We heard about the Genetic Frontotemporal dementia Initiative (GenFI), investigating individuals at genetic risk of FTD. Questions of why FTD versus CBD and PSP are associated with different tau isoforms, and how these differences impact on regional neuropathology, neuroimaging and clinical features remain important research questions.

To conclude the day, Larry Golbe led a discussion about funding priorities in PSP, who funds what research, and whether the research priorities are the right ones. The mission statement of the PSPA 'Working for a World Free of PSP' was undisputed, but there was ground for discussion about the best way to go about doing this. It was interesting to hear a discussion about the mechanisms for maintaining a balanced portfolio of research; investigating questions specific to PSP and CBD, and also developing research into diseases with shared aetiologies and common interest. It was a thought-provoking way to end an enjoyable and educational day. ◆

Spotlight on epilepsy management: focussing on the needs of the individual patient

Highlights of a satellite symposium held at the XXI World Congress of Neurology, 21–26 September 2013, Vienna, Austria

Key points:

- It is important to get the initial AED monotherapy correct in adults with newly diagnosed epilepsy, to improve patient outcomes. The treatment decision should consider the current level of available evidence; for example, the latest ILAE guidance. Furthermore, the initial treatment should look beyond seizure control, by considering patient factors and AED characteristics, to meet the needs of the individual
- It is important to persist in trying alternative AEDs, since novel agents can still provide improvements in seizure frequency and/or severity in previously refractory patients; as with monotherapy, it is important to get the initial adjunctive therapy correct and this should be tailored to the individual patient's needs
- There is a high prevalence of neuropsychiatric comorbidities in patients with epilepsy. Depression in epilepsy may be atypical, underdiagnosed, undertreated and associated with significantly reduced quality of life
- Management of epilepsy needs to include assessment of neuropsychiatric and other comorbidities and treat these with appropriate AED therapy and/or other treatment options
- Now and in the future, epilepsy management should always focus on the needs of the individual patient, in order to optimise their overall health status, functioning and quality of life

Approaches to epilepsy management are constantly evolving as new information about mechanisms underlying this complex condition emerges and more targeted approaches to treatment are developed. The Eisai-sponsored symposium at the recent XXI World Congress of Neurology in Vienna, entitled '*Under the Spotlight: Epilepsy management – are we on the right track?*', took an innovative approach to highlight key issues affecting epilepsy management today and assess the current 'state of play' in this field. Hosted by television health correspondent, Sue Saville, the event involved an interactive panel discussion of international epilepsy experts, who also gave presentations addressing current 'hot topics' in the management of epilepsy.

Professor Michel Baulac (Hôpital Pitié-Salpêtrière, Paris, France) began by discussing the issues involved in the management of adults with newly diagnosed epilepsy, such as the need to correctly diagnose the patient's seizure type and syndrome in order to select the most appropriate antiepileptic drug (AED) treatment, and the crucial importance of getting the choice of initial monotherapy correct. He stressed that AED treatment should be individualised for each patient, looking beyond just seizure control to focus on the individual's overall health status and quality of life. When selecting the most appropriate initial monotherapy, patient factors, such as comorbidities and concomitant medication, and AED factors, such as tolerability and ease of use, must be taken into account. These factors should be considered in conjunction with the current level of clinical evidence available, as outlined in the International League Against Epilepsy (ILAE) recommendations.[1] Professor Baulac highlighted that this guidance has recently been updated to include zonisamide as one of only four AEDs to have level A evidence of efficacy/effectiveness as initial monotherapy for treating partial onset seizures in adults with newly diagnosed epilepsy.[1] This followed the results of a Phase III trial, which demonstrated that once-daily treatment with zonisamide was non-inferior to twice-daily treatment with controlled-release carbamazepine, the most well-established comparator in this setting, in accordance with ILAE guidelines.[2,3]

Professor Elinor Ben-Menachem (Sahlgrenska University Hospital, Gothenburg, Sweden) then outlined challenges involved in the decision-making process for patients who are refractory to monotherapy and require adjunctive treatment with other AEDs. She stressed that adjunctive treatment should only be considered when monotherapy has failed, but pointed out that this occurred in approximately one in three patients.[4] Professor Ben-Menachem again highlighted the importance of tailoring treatment to each patient's particular needs. As when choosing initial monotherapy, selection of an appropriate adjunctive therapy should consider patient factors (e.g. age, comorbidities) alongside AED factors (e.g. side effects, drug interactions, simplicity of use), to ensure the greatest likelihood of medication compliance and treatment success. Professor Ben-Menachem also stressed that, with the dramatic increase in the number of AEDs available over the last 20+ years, there is always the possibility that a novel treatment option may result in improvement in seizure frequency and/or severity, even complete seizure freedom, in previously refractory patients.

Dr Manny Bagary (University Hospital Birmingham NHS Trust, UK) further expanded on the need for a patient-focussed approach to epilepsy management that looks beyond just controlling seizures, with a particular focus on the impact of neuropsychiatric comorbidities on patients' quality of life. Dr Bagary highlighted the high prevalence of neuropsychiatric comorbidities in epilepsy patients, the most common being depression.[5] Although depression in epilepsy has a major impact on quality of life and is associated with an increased risk of suicide, it remains under-recognised and under-treated, largely because it often presents atypically.[5] Dr Bagary stressed that recognition of depression in epilepsy patients can be improved by effective doctor–patient communication and the use of screening tools.[6] Treatment decisions should consider whether the patient's AED therapy can help improve (or at least not worsen) their depressive symptoms, and include the use of antidepressants and/or non-pharmacological approaches. Dr Bagary also highlighted the need for 'real-world' data to complement evidence from clinical trials, in order the help guide AED treatment decisions. He illustrated this by describing a UK clinical audit of the use of eslicarbazepine acetate to treat 201 patients with localisation-related epilepsy in his everyday clinical practice (median dose 800 mg/day; median duration of treatment 12 months).[7] Notably, half of patients experienced ≥50% seizure frequency reduction with eslicarbazepine acetate, almost 20% achieving seizure freedom. Psychiatric and behavioural adverse events were reported in only six (3%) patients, resulting in discontinuation in two patients (1%);[7] the overall safety findings were consistent with the agent's known safety profile.[8]

Professor Eugen Trinka (Paracelsus Medical University, Salzburg, Austria) concluded the symposium by discussing the direction of epilepsy management in the future. Since many patients remain refractory to current treatment options, Professor Trinka highlighted that there is still a need for alternative AED treatment options, particularly those possessing a novel mechanism of action. The latest approved AED is perampanel – a first-in-class, selective, non-competitive AMPA receptor antagonist, which targets post-synaptic excitability. Professor Trinka presented data from his personal experience of using perampanel in clinical practice in 58 patients with partial seizures (median age 44 years; median duration of follow-up 107.7 days), which he concluded was well tolerated, with approximately 20% of patients experiencing 75–100% seizure frequency reduction.[9] He also outlined other exciting advances that are likely to impact epilepsy management in the future, including non-pharmacological treatment approaches, such as experimental devices that detect and/or respond to seizures, cell-based technologies and gene therapy. Professor Trinka concluded by reiterating the theme common to all the presentations and panel discussions – that epilepsy management should first-and-foremost focus on the needs of the individual patient, in order to optimise their overall health status, functioning and quality of life. Within a constantly-changing environment, in which our knowledge base and treatment choices continue to expand, this central focus of epilepsy management remains constant and unchanged.

References

1. Glauser T, et al. Epilepsia 2013;54:551–63.
2. Baulac M, et al. Lancet Neurol 2012;11:579–88.
3. Glauser T, et al. Epilepsia 2006;47:1094–120.
4. Brodie MJ, et al. Neurology 2012;78:1548–54.
5. Kanner AM. Epilepsy Curr 2006;6:141–6.
6. Gilliam FG, et al. Lancet Neurol 2006;5:399–405.
7. Keogh S, et al. Poster presented at XXI World Congress of Neurology, 2013.
8. Zebinix® Summary of Product Characteristics, Eisai Ltd., April 2013.
9. Rohracher A, et al. Poster presented at XXI World Congress of Neurology, 2013.

Date of preparation: October 2013
Nonpro-UK2228

This symposium and article were sponsored by Eisai Europe Ltd

MANAGEMENT OF CHILDHOOD EPILEPSY

ARE WE ON THE RIGHT TRACK?

Highlights of a satellite symposium held at the
10th European Paediatric Neurology Society Congress,
25–28 September 2013, Brussels, Belgium

Key points:

- Challenges of managing childhood epilepsy are heightened by the need to focus on the development of the child, as well as their epilepsy; in particular, by the potential effects of both seizures and AED treatment on the child's neurodevelopment
- There is a need to increase the knowledge base to inform treatment decisions through well-designed clinical trials of AEDs and real-world data in the paediatric population
- Zonisamide is the latest AED to have gained a paediatric license for the adjunctive treatment of partial seizures, approval being based on a randomised controlled trial that followed stringent regulatory requirements
- Since many paediatric patients are refractory to treatment, there continues to be a need for further AEDs, particularly those with novel mechanisms of action
- Perampanel▼ – a first-in-class, selective, non-competitive AMPA receptor antagonist – is the latest approved AED. This has been shown to be efficacious and generally well tolerated as adjunctive therapy in adolescent patients with refractory partial seizures

Management of childhood epilepsy is particularly challenging, since treatment decisions may not only affect a child's current health status, but also their longer-term development. Key issues affecting the management of children with epilepsy were the focus of the Eisai-sponsored symposium at the recent 10th European Paediatric Neurology Society Congress in Belgium, which was entitled '*Management of childhood epilepsy – are we on the right track?*' and chaired by Professor Lieven Lagae (University of Leuven, Belgium).

Professor Helen Cross (UCL Institute of Child Health and Great Ormond Street Hospital, London, UK) began by discussing the challenges associated with diagnosing epilepsy in children, highlighting the complexity of accurate diagnosis among the plethora of childhood syndromes. She stressed the importance of getting the patient's diagnosis correct, since inappropriate treatment may exacerbate the child's seizures. Professor Cross highlighted that children with epilepsy are at an increased risk of cognitive and behavioural problems, the reasons for which are complex and multifactorial. Seizure activity can itself have damaging effects on a child's neurodevelopment, which may already be impaired by their underlying pathology. In addition, antiepileptic drugs (AEDs) may have adverse cognitive and behavioural side effects. Treatment decisions must therefore weigh the potential risks and benefits for each individual child – seizures are not the only consideration. Professor Cross also discussed the challenges involved in providing appropriate management and support to paediatric patients and their families throughout a child's development, including the transition of care from paediatric to adult services.

Dr Stéphane Auvin (Inserm and Hôpital Robert Debré, Paris, France) then focussed on the need for clinical evidence to inform treatment decisions; in particular, the need for different types of evidence – from clinical trials and clinical practice – to provide an overall picture of the likely risks and benefits of a particular treatment approach. He began by highlighting that regulatory requirements for paediatric epilepsy have become increasingly stringent, an important aspect of this being the assessment of an AED's long-term impact on cognition, growth and development. Despite the need for well-designed clinical trials, relatively few have been conducted in the paediatric population to date. The most recent of these was a Phase III trial assessing the safety and efficacy of adjunctive zonisamide for the treatment of partial seizures in children, results of which formed the basis for zonisamide gaining its paediatric license in this setting.[1] In this trial, zonisamide was shown to be well tolerated and significantly more effective than placebo in reducing partial seizure frequency, the proportion of children experiencing ≥50% seizure frequency reduction over the 12-week maintenance period being 50% with zonisamide versus 31% with placebo (p=0.0044).[1] Importantly, an extension study demonstrated that long-term treatment with zonisamide was associated with no consistent detrimental effects on long-term growth and development; overall, no new or unexpected safety signals emerged and the efficacy of zonisamide was maintained over a treatment period of at least 1 year.[2,3] Dr Auvin went on to reiterate that, since clinical trials are conducted under tightly controlled conditions, there is a need for 'real-world' evidence from clinical practice to complement data from clinical trials, illustrating this with a case study of the use of zonisamide in his practice. Dr Auvin also highlighted that clinical trials are difficult to conduct in patients with rare conditions, a problem that has been addressed by the Orphan Drug Law, which lessened the statistical burden for proof of efficacy in Phase III trials, in recognition of low patient numbers. Conditions for which AEDs have been granted orphan drug status include Dravet syndrome and Lennox-Gastaut syndrome. Dr Auvin stressed that there is a particular need for long-term safety surveillance for drugs developed in this way, including the use of registries and evidence from clinical practice, underlining the importance of real-world data.

Professor Elena Belousova (Moscow Institute of Pediatrics and Pediatric Surgery, Russia) discussed the need for further treatment options, particularly those with novel mechanisms of action. She pointed out that, despite the availability of a wide range of AEDs, 20–40% of children fail to respond to their first AED therapy.[4] However, other data have shown that almost one in five patients become seizure free with the addition of an alternative AED after failure of two to five agents,[5] so it is still worth persisting with alternative treatment options in refractory patients. Professor Belousova went on to focus on the latest AED to have gained a license – perampanel – a first-in-class, selective, non-competitive AMPA receptor antagonist. Professor Belousova presented pooled data from three Phase III trials demonstrating that adjunctive perampanel treatment was generally well tolerated and provided improvements in seizure outcomes in adolescent patients (n=143; age 12–17 years) with refractory partial epilepsy over a treatment period of 19 weeks, as per the overall population.[6,7] An extension study demonstrated that adjunctive perampanel continued to be generally well tolerated over a treatment period of up to 12 months, and that its efficacy was maintained throughout treatment, the proportion of patients demonstrating ≥50% seizure frequency reduction ranging from 40–60% during weeks 27–52.[8] Professor Belousova supported these findings with a case study of her personal experience of using perampanel in clinical practice. She concluded by remarking that more recent AEDs are aiming to advance the concept of efficacy (antiepileptic potency) to efficiency (effectiveness plus tolerability), which may translate into improved quality of life for patients.

Despite the considerable difficulties associated with managing childhood epilepsy, an expanding evidence base and advances in drug development are helping to tackle some of these key challenges.

References

1. Guerrini R, et al. Epilepsia 2013;54:1473–80.
2. Guerrini R, et al. Poster presented at 10th European Paediatric Neurology Society Congress, 2013.
3. Rosati A, et al. Poster presented at 10th European Paediatric Neurology Society Congress, 2013.
4. Chu-Shore CJ & Thiele EA. Semin Pediatr Neurol 2010;17:214–23.
5. Schiller Y & Najjar Y. Neurology 2008;70:54–65.
6. Steinhoff BJ, et al. Epilepsia 2013;54:1481–9.
7. Eisai Europe Ltd Data on File PER039.
8. Conry J, et al. Poster presented at 41st Annual Meeting of the Child Neurology Society, 2012.

Date of preparation: October 2013
Nonpro-UK2228

This symposium and article were sponsored by Eisai Europe Ltd

Eisai

Prescribing information is available for perampanel and zonisamide on the page overleaf

PRESCRIBING INFORMATION

Fycompa®▼ (perampanel)
Please refer to the SPC before prescribing.
Presentation: Film-coated tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg perampanel. ***Indication:*** Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older. ***Dose and administration: Adults and Adolescents:*** Starting dose is 2 mg daily. Dose should be titrated based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of between 4mg/day to 12mg/day. Dose should be taken orally once daily before bedtime. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel should be titrated no more frequently than at 1-week intervals. Withdraw gradually. ***Elderly and patients with renal or hepatic impairment:*** Dosage adjustments not required in elderly patients. Dosage adjustments not required in mild renal impairment, not recommended in patients with moderate or severe renal impairment or patients undergoing haemodialysis. Caution in mild or moderate hepatic impairment, titration should not be faster than every 2 weeks and maximum daily dosage not exceeding 8mg. Not recommended in severe hepatic impairment. ***Children and adolescents under 12 years:*** No data available. ***Contra-Indications:*** Hypersensitivity to perampanel or any excipient. ***Pregnancy:*** Not recommended. ***Lactation:*** Unknown if excreted into breast milk. A decision whether to discontinue breastfeeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. ***Warnings and Precautions:*** Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives. There appears to be an increased risk of falls, particularly in the elderly. Cases of aggression have been reported and dose titration should be followed; a dose reduction should be considered in case of persistence of aggressive symptoms. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse. Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, or switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel. Fycompa contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. ***Drug Interactions:*** The possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used. Carbamazepine, phenytoin, oxcarbazepine and topiramate have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Fycompa did not affect in a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid. The effect of perampanel on monohydroxycarbazepine concentrations is not known. Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13% in healthy subjects. Strong inducers of cytochrome P450 such as rifampicin and hypericum are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs and may also reduce perampanel concentrations. Ketoconazole, a CYP3A4 inhibitor, increased perampanel AUC by 20% and prolonged perampanel half-life by 15%. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations. Fycompa used in combination with other central nervous system (CNS) depressants such as alcohol can increase levels of anger, confusion, and depression. The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol. ***Side effects:*** Adverse reactions most commonly lead to discontinuation of perampanel were dizziness and somnolence. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10: decreased appetite, increased appetite, aggression, anger, anxiety, confusional state, ataxia, dysathria, balance disorder, irritability, diplopia, vision blurred, vertigo, nausea, back pain, gait disturbance, fatigue, weight increased, falls. Based on the clinical trial database of 143 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults. ***Legal Category:*** POM ***Basic UK NHS cost:*** Fycompa 2 mg: packs of 7 £35.00, Fycompa 4 mg: packs of 28 £140.00, Fycompa 6 mg: packs of 28 £140.00, Fycompa 8 mg: packs of 28 £140.00, Fycompa 10 mg: packs of 28 £140.00, Fycompa 12 mg: packs of 28 £140.00 **Irish price to wholesaler:** Fycompa 2 mg: packs of 7 €40.95, Fycompa 4 mg: packs of 28 €163.80, Fycompa 6 mg: packs of 28 €163.80, Fycompa 8 mg: packs of 28 €163.80, Fycompa 10 mg: packs of 28 €163.80, Fycompa 12 mg: packs of 28 €163.80 ***Marketing authorisation numbers:*** Fycompa 2 mg 7 tablets: EU/1/12/776/001, Fycompa 4 mg 28 tablets: EU/1/12/776/003, Fycompa 6 mg 28 tablets: EU/1/12/776/006, Fycompa 8 mg 28 tablets: EU/1/12/776/009, Fycompa 10mg 28 tablets: EU/1/12/776/012, Fycompa 12 mg 28 tablets: EU/1/12/776/015. ***Marketing authorisation holder:*** Eisai Ltd. ***Further Information from/Marketed by:*** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN ***Date of preparation:*** September 2013

Adverse events should be reported to Eisai Ltd on +44 (0)208 600 1400/0845 676 1400 or EUmedinfo@eisai.net. In addition, for the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Zebinix® (eslicarbazepine acetate)
Please refer to the SPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily, increased to 800 mg once daily after one or two weeks. Dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients***: Caution. ***Children and adolescents <18years of age:*** Not recommended. **Patients with renal impairment:** Adjust dose according to creatinine clearance (CL_{cr}). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contra-Indications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. Carefully re-evaluate treatment if women become pregnant or plan to become pregnant, and use minimum effective doses. Interacts with oral contraceptives. Use an alternative method of contraception during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** May cause some CNS reactions such as dizziness and somnolence. Do not use with oxcarbazepine. Rash has been reported. Discontinue if signs or symptoms of hypersensitivity develop. Screen for allele HLA-B*1502 in individuals of Han Chinese and Thai origin as this has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Allele HLA-A*3101 has been shown to increase the risk of developing carbamazepine induced cutaneous adverse reactions including Stevens Johnson syndrome (SJS), TEN, Drug rash with eosinophilia (DRESS) or less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular rash in patients of European descent and Japanese populations. Examine serum sodium levels in patients with pre-existing renal disease or who are treated with medicinal products which may lead to hyponatraemia or if clinical signs of hyponatraemia occur. Discontinue if clinically relevant hyponatraemia develops. Do not use in primary generalised seizures. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. ***Drug interactions:*** Has an inducing effect on the metabolism of medicinal products mainly eliminated by CYP3A4 or UDP-glucuronyl transferases, therefore the dose of these products may need to be increased when used concomitantly with Zebinix. May take 2 to 3 weeks to reach the new level of enzyme activity when initiating, discontinuing or changing dose, therefore take time delay into account when using with other medicines that require dose adjustment. Interactions can arise when co-administering high doses with medicinal products that are mainly metabolised by CYP2C19. Carbamazepine: Zebinix dose may need to be increased if used concomitantly with carbamazepine. Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions cannot be excluded. Phenytoin: An increase of Zebinix dose and a decrease of phenytoin dose may be required. Lamotrigine and topiramate: No dose adjustments are required. Valproate and levetiracetam: Concomitant administration appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Oral contraceptives: Interacts with the oral contraceptive. Simvastatin: An increase of the simvastatin dose may be required when used concomitantly with Zebinix. Rosuvastatin: concomitant administration reduced exposure to rosuvastatin. Monitor response to therapy (e.g., cholesterol levels). Warfarin: Can decrease exposure to S-warfarin. No effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. ***Side effects:*** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Serious side effects: hypersensitivity, hyponatraemia, dehydration, grand mal convulsion, ocular hyperaemia, palpitations, bradycardia, hypertension, hypotension, chest pain, epistaxis, liver disorder, drug toxicity, poisoning, Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zebinix 800mg: pack of 30 £136.00. ***Irish price to wholesaler:*** Zebinix 800mg: pack of 30 €143.19. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & C^{a}., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. ***Further Information from:*** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. **Date of preparation**: January 2013

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 Eisai Ltd on +44 (0)208 600 1400/ (0)845 676 1400 or EUmedinfo@eisai.net

Zebinix®: Pregnancy Registry
To provide information regarding the effects of in utero exposure to Zebinix® physicians are advised to enrol pregnant patients taking Zebinix® in the International Registry of Antiepileptic Drugs and Pregnancy (EURAP). More information can be found at the website http://www.eurapinternational.org/. BIAL-Portela and Ca S.A. Sponsors the EURAP Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with antiepilpetic drugs including eslicarbazepine acetate (Zebinix®) and to respond to a requirement of the Committee for Medicinal Products for Human Use (CHMP) to address missing information on safety in pregnancy.

Zonegran® (zonisamide)
Please refer to the SPC before prescribing. ***Presentation:*** Hard capsules: 25 mg, 50 mg, 100 mg zonisamide. ***Indication:*** Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy. Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.
Dose and administration: Adults: Monotherapy: Starting dose is 100 mg once a day. After two weeks, increase to 200 mg once a day. Then increase at two-weekly intervals in 100mg increments. Withdraw gradually. ***Adjunctive therapy:*** Starting dose is 50 mg in two divided doses. After one week, increase to 100 mg daily. Then increase at one weekly intervals in 100mg increments. Can be taken once or twice daily after titration. In renal or hepatic impairment and patients not receiving CYP3A4-inducing agents consider two weekly intervals. ***Paediatric population (aged 6 years and above):*** **Adjunctive therapy:** starting dose is 1 mg/kg once a day. After one week, increase at weekly intervals in increments of 1 mg/kg. In patients not receiving CYP3A4-inducing agents consider two weekly intervals in increments of 1mg/kg. For patients weighing 20 to 55 kg a maintenance dose of 6 to 8 mg/kg once a day is recommended. For patients weighing above 55 kg a maintenance dose of 300 to 500 mg/kg once a day is recommended. Withdraw gradually**.** ***Elderly and patients with renal or hepatic impairment:*** Caution. Not recommended in severe hepatic impairment. ***Contra-Indications:*** Hypersensitivity to zonisamide, sulphonamide or any excipient. ***Pregnancy:*** Do not use during pregnancy unless potential benefits justify the risks. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. ***Lactation:*** Excreted into breast milk. Either discontinue Zonegran or stop breast-feeding. ***Warnings and Precautions:*** Serious rashes occur, including cases of Stevens-Johnson syndrome. Closely supervise and consider discontinuation in patients with unexplained rash. Zonegran contains a sulphonamide group which is associated with serious immune based adverse reactions. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, family history of nephrolithiasis and hypercalcuria. In the event kidney stones occur in paediatric patients, Zonegran should be discontinued. If a hepatic event is suspected, liver function should be evaluated and discontinuation should be considered. Evaluate and monitor serum bicarbonate levels in patients who are at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing Zonegran dose, discontinuing Zonegran treatment or adding alkali treatment with Zonegran as osteopenia may develop. Use with caution in adult patients treated with carbonic anhydrase inhibitors, e.g. topiramate or acetazolamide. Not recommended for use in paediatric patients with other carbonic anhydrase inhibitors. Monitoring of serum bicarbonate levels should be carried out in the paediatric population. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration; avoid excessive temperatures and strenuous physical exercise. Prescribers should draw the attention of patients and their carer to the advice in the PIL (patient information leaflet) on preventing heatstroke and overheating. Discontinuation should be considered in the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature. Co-medication in paediatric patients with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity are not recommended. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Not recommended in paediatric patients who are underweight or have decreased appetite. Weight should be monitored in paediatric patients. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long term effect of weight loss in the paediatric population on growth and development is unknown. Zonegran 100 mg capsules contain E110. ***Drug Interactions:*** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. Interaction studies have only been performed in adults.***Side effects:*** The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. Very common effects (≥1/10): decreased bicarbonate. Common effects (≥1/100, <1/10): decreased appetite, agitation, depression, insomnia, mood swings, anxiety, ataxia, dizziness, memory impairment, somnolence, bradyphrenia, disturbance in attention, paresthesia, diplopia, constipation, diarrhoea, dyspepsia, nausea, vomiting, rash, fatigue, pyrexia, irritability, weight decreased, blood creatinine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). A pooled analysis of safety data on 95 elderly subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus compared to the adult population. Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. Most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, pruritis, alopecia, nephrolithiasis, fatigue, influenza-like illness, pyrexia, oedema peripheral, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, calculus urinary, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms, hypersensitivity-type pneumonitis. The adverse event profile of zonisamide in paediatric patients aged 6 to 17 years in placebo-controlled clinical studies was consistent with that of adults. A pooled analysis of safety data on 420 paediatric subjects has shown a relatively higher reporting frequency of pneumonia, dehydration, decreased sweating, abnormal liver function tests, otitis media, pharyngitis, sinusitis and upper respiratory tract infection, cough, epistaxis and rhinitis, abdominal pain, vomiting, rash and eczema, and fever compared to the adult population (particularly in subjects aged below 12 years) and, at a low incidence, amnesia, creatinine increased, lymphadenopathy, and thrombocytopenia**.** The incidence of a decrease in body weight of 10% or more was 10.7%. In some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation. ***Legal Category:*** POM ***Basic UK NHS cost:*** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. ***Irish price to wholesaler:*** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. ***Marketing authorisation numbers:*** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004.***Marketing authorisation holder:*** Eisai Ltd. ***Further Information from/Marketed by:*** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN ***Date of preparation:*** October 2013.

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 Eisai Ltd on 0208 600 1400/0845 676 1400 or EUmedinfo@eisai.net

European Congress on Treatment and Research In Multiple Sclerosis 2013

Conference details: 2-5 October 2013, Copenhagen, Denmark. ***Report by:*** Dr Julian Furby, Consultant Neurologist, University Hospital Southampton NHS Foundation Trust.

ECTRIMS 2013 was held in Copenhagen. Unfortunately the venue itself was in a slightly bleak concreted district on the edge of the city but the conference centre piqued some interest with its unusual and award winning tilting architectural design. Also impressive was the scale of the occasion with over 8000 delegates and 1200 scientific presentations.

We were in for an unexpected treat with the opening plenary session. Her Majesty the Queen of Denmark (and also patron of the Danish MS society) gave a very informed welcome address. This was followed by a performance from Danish electronic percussion group, Safri Duo. It was a little disconcerting at 09:20 on a Thursday morning to witness several thousand MS researchers clapping their hands in the air to the duos 2001 hit "Played-A-Live". Normal service was promptly resumed with the plenary lecture given by Giancarlo Comi who provided a persuasive argument for treating MS aggressively at the earliest stage, the clinically isolated syndrome (CIS). This would prove to be a common message throughout the conference but there still remains an alarming lack of direct evidence to support this approach.

What causes MS? The big question to which there remains no clear answer. Vitamin D, or the lack of it, and smoking have emerged as risk factors for the development of MS. Dr Ascherio presented data acquired as part of the BENEFIT CIS study which convincingly demonstrated that Vitamin D deficiency (<50nmol/l) at first presentation predisposes to a higher relapse rate and a greater accumulation of T2 lesions over a 5 year period. Epigenetics is also helping to unravel the mysteries of MS causation and gene-environment interactions may explain some of the risk conferred by Vitamin D deficiency. Professor Ebers gave a whistle-stop tour of our current understanding of epigenetics in MS and revealed how it may explain curious epidemiological anomalies such as the rising incidence of MS in females and discrepant ethnic susceptibilities through epigenetic effects on the MHC.

Can we identify patients who are likely to have aggressive disease and might therefore benefit from early aggressive treatment? The Barcelona group has now collected 1000 CIS cases in their observational cohort. Young age, female gender and optic neuritis are all factors associated with a lower risk of conversion to MS and the accumulation disability, whilst oligoclonal band positivity and >3 lesions on MRI confer a higher risk for conversion to MS. Dr

Montelban presented data showing that there are no baseline demographics or clinical factors that can help predict who will respond to treatment. However, ongoing relapses or gadolinium enhancing lesions despite disease modifying treatment are clearly associated with a poorer long-term prognosis. Dr Cohen provided an excellent summary of observational treatment studies in multiple sclerosis that have attempted to determine whether disease modifying treatment delays the onset of progressive disease. Such studies are subject to a number of bias effects and results are conflicting and inconclusive.

Professor Giovannoni explained how the use of biomarkers has revolutionised our management of MS over the years, from oligoclonal bands to neutralising antibodies to JC virus serological testing. CSF neurofilament light chains are now recognised as a useful marker of neurodegeneration in multiple sclerosis. Elevated levels confer a worse prognosis and intriguingly levels fall after treatment with natalizumab or fingolimod. Dr Nishiyami from Japan showed us that CSF glial fibrillary acidic protein can be a useful marker of astrocytic damage in cases of neuromyelitis optica and may help distinguish it from other causes of a longitudinally extensive myelitis, particularly in the occasional cases that are initially seronegative for NMO IgG.

I think I speak on behalf of all MSologists when I say that one of the most difficult aspects of treating multiple sclerosis is in managing the risk of complications, such as PML. It was therefore very welcome to have a session dedicated to this topic. Current practice in treating patients with natalizumab is to stratify the risk of PML according to JCV serology status. Evidence has now emerged to suggest that further stratification can be achieved according to the antibody titre and I am sure this will enter routine practice very soon. In the terrifying situation that a patient might have developed PML, the diagnosis can be achieved with better sensitivity and specificity by using the anti-JCV antibody index in the CSF as opposed to PCR. There has also been recent concern that switching patients from natalizumab to fingolimod (such as those who are JCV positive and have had more than two years of treatment) may result in rebound inflammatory disease activity. Reassuring data were presented by the international MSbase collaboration which showed there may be a slight increase in relapse rate following the switch but that it was proportional to the differential efficacy of the two therapies. However, there were a number of centres with posters showing that their patients had not done so well.

Looking to the future there are a number of molecules for the treatment of MS that are currently in the clinical trial phase or about to hit the market. Of particular interest is Anti-LINGO1 antibody therapy, a novel agent shown to promote remyelination in animal models of inflammatory demyelination and which is now in phase 2 clinical trials. There were few new data on alemtuzumab, dimethyl fumarate, teriflunomide or laquinimod and we now just eagerly await their approvals from the EMA and NICE. ◆

Keele Course on CNS Inflammation

Conference details: 6-8 September 2013, Keele University. ***Report by:*** Thomas Lambert, West Midlands Neurology Trainee, ST4, University Hospital of North Staffordshire, Stoke-on-Trent.

As the country was blanketed in a layer of cold misty weather, appearing to herald the end of summer, around 120 delegates gathered at the peaceful Keele University campus in North Staffordshire for the 3rd biennial "Keele Course on CNS Inflammation".

The first afternoon began with Professor Neil Robertson from University Hospital of Wales, Cardiff giving an excellent review of CNS vasculitis, reminding us that this is a rare diagnosis but also covering the range of important differentials.

Dr Abhjit Chaudhuri (Queen's Hospital, Romford) talked about ADEM and mimics which nicely led onto a history and up to date review of NMO spectrum disorders from Dr Jacqueline Palace (John Radcliffe Hospital, Oxford). With the increasing utilisation of the anti-anquaporin-4 antibody assay (which is available via Oxford, free of charge for all NHS patients from England and Scotland) this spectrum of disorders is becoming increasingly recognised and the existing NMO diagnostic criteria may well have to be revised. The importance of differentiating this condition from MS with regard to prognostication and treatment decisions was emphasised.

Friday afternoon closed with the legendary Professor Angela Vincent (John Radcliffe Hospital, Oxford) providing a state of the art review of CNS Antibody-Mediated Diseases, emphasising the clinical features associated with various pathological antibodies but also reminding us that as we learn more about them and test for them more widely, the phenotype is widening.

Saturday morning began with Professor John Zajicek (Peninsula Medical School, Plymouth) delivering an excellent review of the diagnosis and treatment of neurosarcoidosis. We were reminded that this diagnosis can be difficult and perhaps is underdiagnosed. The importance of obtaining a CNS biopsy to confirm the suspected diagnosis was emphasised with a reminder that systemic sarcoidosis can co-exist with other pathologies affecting the CNS. Professor Zajicek's previously published case series and diagnostic criteria are recommended reading. The importance of imaging the whole neuro-axis with gadolinium enhancement was emphasised. Enhancement in the lumbar spine may be a much more amenable biopsy target than the brain so should always be looked for when neurosarcoidosis is suspected. It is very rare to have normal CSF in neurosarcoid and a mirror pattern of oligoclonal bands (OCBs) is often seen although sometimes OCBs are seen in CSF only. One case was shown in which a thoracic cord PET scan revealed a lesion which was not seen on MRI although it is unlikely that this will become part of routine clinical investigation.

Saturday morning continued with Professor Cris Constantinescu (Queen's Medical Centre, Nottingham) reviewing the current evidence base for the expanding range of disease modifying treatments (DMTs) in MS. The current target for DMTs in MS being inflammation, leaves other pathological processes (demyelination, axonal loss, gliosis and remyelination) untargeted. With the likely clinical correlate of inflammation being relapses, the evidence of their reduction in RRMS provides the basis for most of the evidence for current DMTs. Alternative outcome measures such as sustained disability progression and time to EDSS 4 for EDSS 6 were also discussed. Discussion included when to start DMT and that it was probably not cost-effective to start DMT for all cases of clinically isolated syndrome such as 1st presentation of optic neuritis but accurate risk stratification may in the future be able to identify those individuals that are more likely to benefit from early DMT.

The MS theme continued on Saturday morning with Professor Gavin Giovannoni (Barts and The London Medical School) speaking on MS Diagnostic Pitfalls. The philosophical idea of a disease as a clinic-pathological entity was explored with a history of the definition of MS and the observation that the clinical definition of MS is evolving. MS mimics and red flags such as negative OCBs, raised CSF protein or CSF pleocytosis and systemic symptoms and signs such as uveitis, age >50, neuropsychiatric symptoms and peripheral nerve involvement were good take home points. Another useful learning point was that all cases of suspected primary progressive MS should be screened for adrenomyeloneuropathy by testing urine for long chain fatty acids.

Dr David Hunt (Institute of Genetics and Molecular Medicine, Edinburgh) used some recent cases of atypical haemolytic uraemic syndrome and some impressive detective work which linked them to a new beta interferon formulation to demonstrate the unknown complications of new biological therapies. This need for all of us treating patients with biological therapies to be continually vigilant is also emphasised in the story of Natalizumab-associated PML which he brought us all up to date on.

Three SpR and Consultant case presentations led us nicely up to lunch.

Saturday afternoon kicked-off with Dr Martin Duddy (Royal Victoria Infirmary, Newcastle) who provoked thought about the consideration of starting DMT early in the disease such as for patients with Clinically Isolated Syndrome. Under the UK Risk Sharing scheme DMT treatment of CIS is due to be commissioned and clinicians will individually have to weigh up the limited and likely never to be complete evidence and come to a conclusion.

Dr David Rog (Salford Royal Hospital, Manchester) continued the theme of uncertainty in DMT treatment of MS with a talk on Benefit and risk in MS treatment. The risk of PML in Natalizumab treatment and risks and safety in Fingolimod initiation and treatment and the need for more direct comparative and meaningful outcomes in MS studies were discussed.

Professor Clive Hawkins (UHNS, Stoke-on-Trent) gave a comprehensive review of optic neuritis and its differential diagnoses.

Dr Adnan Al-Araji (UHNS, Stoke-on-Trent) presented a comprehensive review of Neuro-Behcet's, covering its pathological feature, clinical manifestations and treatment. Previous diagnostic criteria were discussed and soon to be published new diagnostic criteria and management guidelines were presented.

Saturday ended with three further interesting clinical case presentations.

Sunday began with an excellent review of the use of laboratory tests in the diagnosis and management of CNS neuro-inflammatory disorders by Dr Saiju Jacob (Queen Elizabeth Neuroscience Centre, Birmingham). One future study to look out for was mentioned, a prospective study of screening for autoantibodies in new onset psychosis which is being planned in Birmingham.

Dr Hadi Manji (Queen's square, London), in a talk entitled, HIV and the Brain - 30 Years of an Epidemic, gave us the benefit of his vast experience and learning over the years in HIV associated neurological presentations. His take home messages were: to think of HIV in any neurological presentation, particularly inflammation or a chronic problem; a reminder that HIV serology may be negative at presentation; and to think about CSF escape syndrome (requiring changing of anti-retrovirals to those with good CNS penetration and IRIS). For a good review of the topics covered in his his talk there is an article of his in JNNP. Finally, the course ended with a few more case presentations.

Overall, this was an excellent weekend with many useful learning points and the promise of developments in the field of CNS inflammation to make it well worthwhile coming back for the 4th course in two years' time. Being a local trainee I may be accused of bias but I think all people I spoke to felt it was a well-run course with many excellent speakers and topic. Many thanks Dr Al-Araji and team! ◆

The Third World Parkinson Congress

Conference details: 1-4 October 2013, Montréal, Canada. ***Report by:*** Professor Roger Barker, , Professor of Clinical Neuroscience at the University of Cambridge and Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair.


Ray Chaudhuri


Alan Parkinson Project Play


Tango Class

Following on from the success of previous WPCs in Washington and Glasgow, the third such congress took place in the autumnal sun of early October in Montréal and sought once more to bring patients, carers, medical practitioners, scientists and therapists together under one roof to discuss one condition- Parkinson's disease (PD). The ambition of the congress is to enable the dialogue and better understanding of the diseases by linking those with the condition and those seeking to help treat it at whatever level. As such the programme is an interesting mix – ranging from detailed science to live performances of patient inspired artistic endeavours. Each day began with hot topics picked from the numerous posters and was followed by plenary sessions that tackled a host of topics but which in summary covered:

- The prion like behaviour of alpha synuclein and how this may modify our thinking about disease pathogenesis and spread, as well as therapeutically;
- The genes linked to PD and how they may need to be expressed through environmental risk factors and the role, if any, of inflammation in this process;
- The extent and significance of non-motor symptoms in patients at diagnosis and through the disease course;
- The cognitive deficits seen in PD, their basis and imaging correlates and how this relates to the development of the dementia of PD;
- The new therapies being tried in PD including cell, gene and environmental / exercise based approaches;
- The importance of the patient in driving their own care and research and how this can best be achieved in the context of multi-disciplinary teams.

This was followed by a special lecture including the inaugural James Parkinson lecture delivered by Warren Olanow, who eloquently took us through the history of discovery in PD including the original videos of Hornykiewizcz showing the effects of dopa in a patient with PD in the early 1960s – an experiment that could now not be done without a huge amount of paperwork and approval! Thereafter there were a collection of parallel sessions and workshops that covered a plethora of topics including protein misfolding, mitophagy and new gene / cell based approaches.

So in summary the major take home messages were:

- That PD may begin as a disorder outside of the CNS that is triggered by a misfolding of alpha synuclein which then spreads and causes pathology along neural networks through a prion like behaviour with an early synaptic pathology;
- The cellular pathology of PD involves a dynamic interplay between proteins, leading to altered mitochondrial and lysosomal function, which may create a positive feedback on alpha synuclein aggregation accelerating the disease process in some cells;
- The non motor features of PD, especially many of the cognitive abnormalities, significantly impact on quality of life and need to be better recognised, their basis defined and their treatment improved;
- The ability to treat PD through environmental and physical therapies needs to be aggressively pursued as it holds much promise and may be a very effective intervention at all stages of disease and should not be trumped by more "sexy" therapies involving genes, cells and small molecules. ◆

3rd Parkinson's Review Meeting

Conference details: Thursday 10th October 2013, Academy of Medical Sciences, London.
Chair: Professor Kailash Bhatia
Review by: Sharron Greatorex, Genus Pharmaceuticals

The third annual Parkinson's Review Meeting (PRM) was held at the Academy of Medical Sciences in Portland Place, London and was supported by an unrestricted grant from Genus Pharmaceuticals Ltd. Discussions were chaired by Professor Kailash Bhatia, Professor of Clinical Neurology at UCL and Honorary Consultant Neurologist at London's National Hospital for Neurology & Neurosurgery. The opinions expressed in this article are not necessarily those of the publisher or Genus Pharmaceuticals

The meeting was opened by Dr Thomas Foltynie, Consultant Neurologist and Senior Lecturer at the National Hospital for Neurology & Neurosurgery. To deliver optimal care, quality standards should ensure that each Parkinson's patient has access to a PD specialist and specialist nurse alongside a multidisciplinary team (MDT) and non-drug treatments. There are a number of options available when patients' Parkinson's cannot be controlled on oral therapies alone. APO-go is indicated in patients whose disease is not sufficiently controlled by oral anti-Parkinson medication. Other advanced treatments are available: apomorphine infusion via pump, Deep Brain Stimulation (DBS) and levodopa intestinal gel. Mode of administration is also a factor as apomorphine can be given as intermittent injections or as a continuous subcutaneous pump infusion and DBS can target different areas of the brain.

Dr Jon Stamford (Scientific & Advocate Communication Coordinator for the Cure Parkinson's Trust) and Brian Corbin gave frank and rather moving accounts of their patient experience as sufferers of PD. Jon explained how NMS had affected his quality of life, but agreed that no two patients were symptomatically alike making a 'one size fits all' treatment algorithm unfeasible. Brian explained how personalised treatment has allowed him to return to work, in particular the huge support provided by his PD nurse specialist. "All PD patients have the right to a specialist nurse", he added.

Professor K Ray Chaudhuri, Consultant Neurologist and Professor in Neurology/Movement Disorders at King's College Hospital NHS Foundation Trust, then spoke about how motor and non-motor symptoms (NMS) of PD cause poor quality of life for patients and their caregivers, yet NMS tend to be under-recognised and under-treated. Khoo *et al*.[1] studied the frequency of NMS in a newly diagnosed PD patient cohort and found that symptoms such as impairment of olfaction, REM loss of atonia, REM sleep behaviour disorder (RBD), constipation, depression, colour vision effects, pain and excessive daytime sleepiness (EDS), were common, reflecting the multi-system nature of the disorder.

Newly released results from the AM IMPAKT[2] study described the effect of apomorphine s.c. injection in PD patients with (the often under-recognised) morning akinesia resulting from delayed or unreliable onset of effect of their first morning dose of levodopa. By circumventing the oral route, apomorphine s.c. injection provided rapid and reliable turning-ON for patients with morning akinesia, reducing time-to-on by an average of 40 minutes. Professor Chaudhuri's presentation closed with an emphasis on how as well as motor-related symptoms, NMS and multi-morbid conditions can be a significant burden for Parkinson's patients.

Seema Buckley, Chief Pharmacist at NHS Kingston Clinical Commissioning Group (CCG) discussed the payer perspective and how any commissioned PD services need to innovate to improve quality whilst reducing cost. This comes in the wake of July's NHS call to action requesting CCGs make further savings of £30billion on top of Sir David Nicholson's QIPP efficiency savings challenge. NHS England will implement consistent national policies, but the CCGs may allow for variability based on local health needs.

The next speaker, presenting the business manager's perspective for coding the PD pathway using the best practice tariff was Alexa Coombes, Neurology Business Manager for UCL Hospitals NHS Trust. Historically, the system was made based on Healthcare Resource Group (HRG) codes, which does not always reflect pathways or specialist centres and leaves little scope for innovation. Alexa explained that system revisions had assigned a cost per patient episode based on bed-days, consumables, medical /nursing or scientific staff time, radiology and diagnostics and consequently, adjusted HRG codes for many specialist areas have been introduced. The new integrated commissioning framework splits care into a multi-tiered generic service model (involving local community and primary care, MDT specialist outreach clinics and specialist care hubs to undertake a full range of neurology-related procedures).

Charles Rendell, London Regional Commissioning Advisor at Neurological Commissioning Support (NCS) outlined some of the new organisations within the NHS including 12 Strategic Clinical Networks (SCNs) and Clinical Senates. The new networks are: cancer; cardiovascular including renal, diabetes and stroke; maternity, children and young people; and, mental health, dementia and neurological conditions (as lobbied for by NCS). SCNs could be key for improving neurology services and Charles urged participants to build their awareness of local activities within their SCN and take an active lead in commissioning decisions.

Professor Chaudhuri spoke about setting up a complex Parkinson's referral service. In Professor Chaudhuri's Trust they have used the 2011 Parkinson's Audit from Parkinson's UK as a benchmark when designing their referral service. Professor Chaudhuri thought that despite a genuine need to iron out national quality differences, ideally there should be nominated centres of excellence for PD and devolved areas which refer to these centres. To facilitate this type of hub-and-spoke model would require the involvement of GPSIs in neurology and Parkinson's Specialist Nurses and collaboration between Parkinson's services and geriatric care would benefit referral services.

Allan Karr, Pharmacy Business Manager of UCLH and Chairman of the National Homecare Medicines Committee outlined how homecare can support PD patient outcomes. For patients homecare can mean increased choice, reduced waiting times, travel and hence increased convenience. Homecare currently covers a multitude of therapeutic areas including PD where apomorphine is regularly supplied by homecare.

The PRM included frequent audience and panel questions and keypad voting and it was very encouraging to hear such passionate opinions and valuable knowledge and experience being shared.
For further information on the day's talks and outcomes or if you would like to know more about other PRM events taking place throughout the UK, please contact prm@genuspharma.com.

References

1. Khoo TK Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. Neurology 2013; 80: 276-281

2. For study information see: http://www.acnr.co.uk/2013/05/news-review-6/ (last accessed;:23 October 2013)

APO-1013-1934
Date of preparation: October 2013

This review has been provided by Genus Pharmaceuticals and they have sponsored its inclusion in ACNR.

GENUS PHARMACEUTICALS

For rapid relief from 'off' periods in Parkinson's disease

APO-go® Apomorphine hydrochloride
PRESCRIBING INFORMATION Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropyschiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision:** September 2013
For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

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

Version Number: APG.PI.V19 **Date of preparation:** September 2013 **APO-0912-1902**

APO-go® PEN
apomorphine hydrochloride

Stay 'on'

Continuity of Care in the Management of Prolonged, Acute, Convulsive Seizures in Children:

a review of guidelines and epilepsy specialist nurses' opinions

Christine Bennett,

BSc Hons, is a children's Epilepsy Specialist Nurse (2000-present) and an Independent Nurse Prescriber. She has worked with the Department of Health on several projects to improve epilepsy services. She is also a part-time lecturer at Leeds Metropolitan University (2008-present). Currently, she is developing a Paediatric Epilepsy Training foundation course with the Royal College of Paediatrics and Child Health.

Professor Helen Cross,

is The Prince of Wales's Chair of Childhood Epilepsy and Honorary Consultant in Paediatric Neurology at UCL-Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London and Young Epilepsy, Lingfield. She is currently Clinical Advisor to the Children's Epilepsy Surgery Service, and Secretary General of the International league Against Epilepsy. She is on the Editorial Board of *Epileptic Disorders, Developmental Medicine Child Neurology* and *European Journal of Paediatric Neurology*.

Correspondence to:
Christine Bennett. BSc Hons
The Children's Centre
70 Walker Street
Hull HU32HE
Tel: 01482 886518
Fax: 01482 221261
Email: Christine.Bennett@hey.nhs.uk

Conflict of interest statement:
This research was supported financially and co-authored by ViroPharma SPRL. All authors are members of the Steering Committee of the PERFECT™ initiative, which is managed and funded by ViroPharma SPRL. The authors would like to thank the following Steering Committee members, Alexis Arzimanoglou, Ettore Beghi, Lieven Lagae, Janet Mifsud, Dieter Schmidt, Arun Mistry and Gordon Harvey for their time and expertise in reviewing the manuscript. All Steering Committee members, or their respective departments, received honoraria from ViroPharma SPRL for participating in the Steering Committee, apart from Gordon Harvey and Arun Mistry who are ViroPharma employees. Editorial support was provided by Godfrey Lisk of PAREXEL, and was financially supported by ViroPharma SPRL.

Provenance and peer review:
Commissioned and externally peer reviewed

To cite:
Bennett C, Cross H ACNR2013;V13:6:36-38

Summary:

- Clearer information is needed on prolonged, acute, convulsive seizures
- All children with a history of prolonged, convulsive seizures should have an individual health care plan
- There need to be clearer links between health and educational sectors
- There should be systematic training of all community caregivers, including teachers
- Comprehensive clinical guidelines are needed to ensure children are treated as quickly as possible wherever a prolonged convulsive occurs in the community

Epilepsy has a median incidence rate of 82.2 per 100,000 people, including children.[1] Approximately 20% of individuals with epilepsy are refractory to treatment[2] and at increased risk of breakthrough seizures. Some are prone to prolonged, acute, convulsive seizures and the risk of proceeding to status epilepticus if timely treatment with rescue medicine is not administered. Given that most breakthrough seizures occur outside hospitals, the National Institute for Health and Clinical Excellence (NICE) guidelines recommend a comprehensive care plan for people with epilepsy and training of non-healthcare professional caregivers in the administration of rescue medication. NICE also stresses that epilepsy specialist nurses should play an integral role in the treatment of epilepsy.[3]

Current management of children at risk of prolonged, acute, convulsive seizures in the community has not been well studied, but recent surveys of epilepsy services for children identified significant gaps in service provision in the UK.[4,5] Epilepsy specialist nurses play an important role in the care plan for children with epilepsy, providing clinical management and a bridge between schools, parents and healthcare professionals. According to the Epilepsy[12] national audit, and contrary to NICE guidelines advice, 47% of the epilepsy services audited do not have an epilepsy specialist nurse, and only 59% have an epilepsy clinic for young people and teenagers.[4]

Within this context, the Practices in Emergency and Rescue medication For Epilepsy managed with Community administered Therapy (PERFECT™) initiative was set up to explore how prolonged, acute, convulsive seizures are managed in the community in six European countries, including the UK. This paper discusses the first two phases of the PERFECT™ initiative, specific to the UK, with a particular focus on the findings relating to perceptions of epilepsy specialist nurses.

Methods

The first phase of the PERFECT™ initiative involved a desk-based review of clinical guidelines, policies and legal frameworks governing the administration of rescue medication to children in non-hospital settings.[6] The second phase included a survey of health care professionals to gauge perceptions of care received by children outside of hospital. Twenty-nine health care professionals, including 10 epilepsy specialist nurses, were interviewed in the UK.

Results

Clinical Guidance

The policy analysis showed that, in the UK, management guidelines for prolonged, acute, convulsive seizures at the national level focus primarily on hospitals. Table 1 provides a list of current clinical guidelines and Table 2 outlines the key points of existing clinical and non-clinical guidance.

NICE issued guidelines specific to the management of prolonged, acute, convulsive seizures in community settings in the UK. In addition to the recommendations described above, they specify preferred treatments for prolonged, acute, convulsive seizures: buccal midazolam as first-line treatment in "children, young people, and adults with prolonged or repeated seizures in the community" and rectal diazepam "if preferred, or if buccal midazolam is not available".[3]

Table 1: Current clinical guidelines and their audiences

Audience	Guideline(s)
Hospital setting (i.e., Accident and Emergency, Intensive Care Unit departments)	APLS guidelines[15] SIGN 81 (2005)[16] NICE guidelines (updated 2012)[3]
UK Ambulance Service	Joint Royal Colleges Ambulance Liaison Committee guidelines[17]
Community setting (e.g., schools)	NICE guidelines (updated 2012)[3]

APLS, Advanced Paediatric Life Support; SIGN, Scottish Intercollegiate Guidelines Network; NICE, National Institute for Health and Clinical Excellence.

Non-clinical guidance

The most relevant guidance to schools is offered by the Department of Health and Education, and refers to medication management in schools.[7-9] This guidance describes how medicines should be administered to children with chronic disease in mainstream schools and what processes to follow. Most of this guidance, however, requires updating to be more specific to the management of children at risk of prolonged, acute, convulsive seizures. In our survey, we found that physicians and epilepsy specialist nurses were largely unaware of existing guidelines or legal frameworks relating to the treatment of children at risk of prolonged, acute, convulsive seizures in schools and other community settings. A paediatrician described the situation for school personnel as "a grey area" and one epilepsy specialist nurse surveyed stated, "Carers and teachers are in a vulnerable position when giving meds [medication] to other people's children, so guidelines would be very helpful to clarify".

The current chain of care

Health care professionals surveyed appeared to have limited knowledge of whether children who have been prescribed rescue medication for prolonged, acute, convulsive seizures actually receive this medication following discharge from hospital. They also found it difficult to estimate the number of patients managed in the community versus the hospital. Regarding seizure records, one neurologist described them as "very helpful" in making dose adjustments to patients' medication; however, respondents stated that information about seizures occurring outside of the hospital may not be captured in detail. One epilepsy specialist nurse explained: "…some parents feel they do not need to write it down as they know how many seizures per month the child has, other children have so many seizures per day that the parents feel they could not possibly record the number".

Epilepsy specialist nurses surveyed stated that their responsibilities included advising junior doctors on treatment choice, teaching families to administer rescue medicine and providing training to schools. Physicians have little time to coordinate care with schools, and rely on epilepsy specialist nurses to meet this need. Epilepsy specialist nurses surveyed believe that, because of their unique position as intermediaries between doctors and parents/caregivers, they are better placed to understand the needs of caregivers outside of the hospital, to advise physicians on treatment choice and to implement care plans. Key findings regarding the perceived roles of epilepsy specialist nurses, as reported by survey respondents, are summarised in Table 3.

Table 2: Overview of the main clinical and non-clinical guidelines

Clinical guidance

1. NICE 2012 guidelines recommend buccal midazolam as first-line treatment[3]
2. Joint Royal Colleges Ambulance Liaison Committee guidelines instruct paramedics on how to act after midazolam has been administered to a child by a parent or other caregiver; however, they are not permitted to carry, or administer to patients, any controlled substance such as buccal midazolam[17]

Non-clinical guidance

3. Parents, caregivers and teachers may administer rescue medication as long as:
   a. They have received specific training[7-9]
   b. They follow previously agreed protocol[7-9]
4. It is not a legal requirement for school staff to administer medicines to children[7-9]
5. Schools should ensure that they have sufficient numbers of staff trained to administer emergency medicines, or make alternative arrangements with the local health service[7-9]
6. Schools must ensure that training is provided to all those who volunteer to administer medicines[7-9]
7. Schools must have an epilepsy policy as part of their obligation to meet the requirements of the Disability Discrimination Act[7-9,14]

NICE, National Institute for Health and care Excellence.

Table 3: Overview of the key findings from the PERFECT™ initiative HCP surveys

Key findings

1. EPILEPSY SPECIALIST NURSEs have some influence over which treatments physicians prescribe. This tends to be buccal midazolam because of convenience; in schools, teachers are generally unwilling to administer medication rectally. However, EPILEPSY SPECIALIST NURSEs can advise on alternatives to buccal midazolam when required. The nurse's role, therefore, is predominantly one of training (when the hospital/practice has an EPILEPSY SPECIALIST NURSE)
2. The perceived role of the EPILEPSY SPECIALIST NURSE is to:
   a. Inform and educate patients and caregivers, and answer questions about how to manage seizures in the home and the wider community. To reiterate and cover gaps in knowledge
   b. Inform and educate the wider community, including schools, and instill confidence to administer rescue medicine
   c. Teamwork approach alongside physician and caregiver

Training in schools and other community settings

In the UK, training on the administration of rescue medication and resources for schools are made available by voluntary sector organisations such as Epilepsy Action and Young Epilepsy. The Joint Epilepsy Council provides training and an online repository of information for trainers that are used broadly across community settings. (http://www.community-epilepsy-services.co.uk/training.html)

Physicians believe that they have a responsibility to educate and train, but because of time constraints, this is limited to training parents. The physicians assume that parents will then provide training to schools and other non-clinically trained caregivers in the community. Epilepsy specialist nurses often assume the responsibility of liaising with, and educating personnel in schools and the wider community. However, limited availability of epilepsy specialist nurses and lack of availability of a licensed rescue medication with a route of administration suitable for use in the community, were cited by physicians and epilepsy specialist nurses as barriers to on-site treatment of prolonged, acute, convulsive seizures in the community. Epilepsy specialist nurses also believe that lack of, or inadequate training of, teachers/main caregivers often results in unnecessary ambulance call-outs and/or inaction due to fear of liability and/or fear of doing harm.

Discussion

Findings from the PERFECT™ initiative highlight that health care professionals have low awareness of how children at risk of prolonged, acute, convulsive seizures are managed in the community, which can be compounded by a lack of accurate recording of seizures. Health care professionals have little engagement with schools and other community settings, and this role is traditionally taken on by epilepsy specialist nurses. The involvement of epilepsy specialist nurses in patient care has been shown to result in reduced hospital admissions, better management of physician time so that they are able to focus on more complex cases, reduced visits to GPs and improved patient self-management.[4,10]

Despite NICE recommendations that all patients with epilepsy have access to an epilepsy specialist nurse, 47% of paediatric departments in the recent Epilepsy[12] audit did not.[4] These findings were confirmed in our survey. Sufficient funding and provision of epilepsy specialist nurses is fundamental in ensuring a seamless transition from hospital to outpatient care for children with epilepsy[10] and providing children and their parents with the support they need to help them more effectively manage their condition outside of hospital.

The NICE guidelines are unique in Europe in that they provide detailed guidance on the administration of rescue medication to children with a history of prolonged, acute, convulsive seizures outside of the hospital.[3,11,12] They call for a comprehensive care plan for all children and young people with epilepsy, and training for non-clinically trained caregivers in the community on the administration of rescue medication.[3,12] However, guidelines alone are insufficient to improve the management of children at risk of prolonged, acute, convulsive seizures. Their correct implementation requires the provision of clear information to parents, schools and other non-clinically trained caregivers on prolonged, acute, convulsive seizures and their management, and training on the administration of rescue medication. The lack of a licensed rescue treatment was highlighted as a barrier to on-site treatment of prolonged, acute, convulsive seizures in the community; however, since the PERFECT™ health care professional survey was conducted, a licensed treatment, Buccolam® (midazolam oromucosal solution) has become available in the UK for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (aged from 3 months to <18 years).[13]

Training on epilepsy management and timely administration of rescue medicine would instil confidence in school staff, and facilitate the implementation of a care plan for each child at risk of prolonged, acute, convulsive seizures enrolled in the school. The Epilepsy Action 2012 school survey found that 25.8% of teachers had not had epilepsy training in the last three years. Mainstream schools are required to appoint a Special Education Needs Coordinator (SENCO);[14] as a teacher, the SENCO has the best insight into the needs of school personnel and can work with epilepsy specialist nurses to ensure that teachers and school nurses receive adequate in-house training and education on seizure management.

Table 4: Recommendations from the PERFECT™ initiative Steering Committee for improving treatment outcomes and addressing the treatment gaps in current management of PROLONGED, ACUTE, CONVULSIVE SEIZURES in the community

Recommendations

1. Raise awareness among physicians regarding the current inconsistent management of PROLONGED, ACUTE, CONVULSIVE SEIZURES in the community setting
2. Develop realistic guidelines that integrate the role of EPILEPSY SPECIALIST NURSEs and limit the burden placed on physicians
3. Create new training materials that incorporate feedback from HCPs, patients and caregivers, and that use an interactive approach (e.g., DVDs, web-based training). An EPILEPSY SPECIALIST NURSE [surveyed] said "What we are missing is a decent DVD that shows midazolam administration for parents. We have had various commercial ones but not been totally satisfied with them. This is because professionals have not been quite as involved. Also, a coloured booklet/leaflet might be useful."
4. Ensure consistent training in schools through standard formal guidelines and protocols
5. Encourage discussion of how to fill gaps in PROLONGED, ACUTE, CONVULSIVE SEIZURES management by publicising the benefits of EPILEPSY SPECIALIST NURSEs, such as:
   a) Addressing patient/caregiver questions and providing practical support
   b) Providing training to the community at large, including schools
   c) Allowing physicians to focus on patient care in the clinical setting

PROLONGED, ACUTE, CONVULSIVE SEIZURES, prolonged, acute, convulsive seizures; HCPs, healthcare practitioners.

Leveraging insights gained through the PERFECT™ initiative, additional recommendations are detailed in Table 4. The next stage of our research involves a survey of children with prolonged, acute convulsive seizures and their caregivers in the UK and five other European countries in order to explore their perspectives on the quality of care received for prolonged, acute convulsive seizures in community settings. This survey will report in early 2014 and should help improve our understanding of existing gaps that should be addressed in the management of this group of children with epilepsy in community settings.

Summary

Prolonged, acute, convulsive seizures pose a serious risk to children with epilepsy, highlighting the need for a comprehensive management plan that addresses both the hospital and community settings such as schools to ensure that children at risk of prolonged, acute, convulsive seizures receive their rescue medication as quickly as possible, regardless of where their seizure occurs. When present, epilepsy specialist nurses function as a much-needed link between these settings and may improve the quality of care overall for patients. Surveys conducted as part of the PERFECT™ initiative confirm the essential role of the epilepsy specialist nurse and reveal the need for consistent guidelines, additional information and training materials to help facilitate the management of prolonged, acute, convulsive seizures in schools and other community settings.

REFERENCES

1. Kotsopoulos IA, et al. *Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures.* Epilepsia 2002;43(11):1402-9.
2. Schmidt D, Sillanpaa M. *Evidence-based review on the natural history of the epilepsies.* Curr Opin Neurol 2012;25(2):159-63.
3. National Institute for Health and Clinical Excellence (NICE). *Clinical Guidelines,CG137: The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care.* NICE 2012:1-636.
4. Dunkley C, et al. *EPILEPSY 12: United Kingdom collaborative clinical audit of health care for children and young people with suspected epileptic seizures.* Available at: http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Epilepsy12-Full-National-Report-pub-2012.pdf. Last accessed 10 January 2013.
5. Smithson WH, Hanna NJ. *Deaths from epilepsy: what next?* Br J Gen Pract 2002;52(483):795-6.
6. Wait S, et al. *The administration of rescue medication to children with prolonged acute convulsive seizures in the community: what happens in practice?* Eur J Paediatr Neurol 2012;17(1):14-23.
7. Department for Education and Skills. *Managing Medicines in Schools and Early Years Settings.* Available at: https://www.education.gov.uk/publications/standard/publicationDetail/Page1/DFES-1448-2005. Last accessed 21 February 2013.
8. Department for Health Social Services and Public Safety, Department for Education. *Supporting Pupils with Medication Needs 2008.* Available at: http://www.deni.gov.uk/support_with_medical_needs.pdf. Last accessed 21 February 2013.
9. The Scottish Executive. *The Administration of Medicines in Schools 2001.* 2001. Edinburgh: The Scottish Executive.
10. Irvine F, et al. *Best care: The value of epilepsy specialist nurses.* Available at: http://www.epilepsy specialist nursea-online.org.uk/documents/FV%20Best%20care%20Jul2010.pdf. Last accessed 21 January 2013.
11. Kalviainen R. *Status epilepticus treatment guidelines.* Epilepsia 2007;48 Suppl 8:99-102.
12. Lagae L. *Clinical practice: the treatment of acute convulsive seizures in children.* Eur J Pediatr 2011;170(4):413-8.
13. ViroPharma SPRL. *Buccolam 2.5 mg oromucosal solution: summary of product characteristics.* Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002267/WC500112310.pdf. Last accessed 24 April 2013.
14. Department for Education and Skills. *Special Education Needs Code of Practice.* Available at: http://www.education.gov.uk/aboutdfe/statutory/g00213170/special-educational-needs-code-of-practice. Last accessed 20 February 2013.
15. Advance Life Support Group. *Advanced Paediatric Life Support (APLS)* Fifth Edition. 2011.
16. Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of epilepsies in children and young people: A national clinical guideline.* SIGN 2005:1-57.
17. Joint Royal Colleges Ambulance Liaison Committee. *UK Ambulance Service. Clinical Practice Guidelines.* Available at: http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/prehospitalcare/jrcalcstakeholderwebsite/guidelines. Last accessed March 2013.

In seconds, Emily will have a seizure. In minutes, her grandmother could stop it.

BUCCOLAM® (midazolam oromucosal solution) is the first and only licensed oromucosal midazolam for prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years).[1]

BUCCOLAM is suitable for use in situations when a rapid onset of action and fast recovery are required.[1]

For more information, please visit **www.BUCCOLAM.co.uk**.

Reference: 1. ViroPharma SPRL. BUCCOLAM Summary of Product Characteristics

ViroPharma™

BUCCOLAM™
MIDAZOLAM OROMUCOSAL SOLUTION

BUCCOLAM® (midazolam oromucosal solution) Abbreviated Prescribing Information (UK version)

Please refer to the Summary of Product Characteristics (SmPC) for full product information.

BUCCOLAM® (midazolam oromucosal solution)

Presentations: Pre-filled oral syringes containing 2.5 mg, 5 mg, 7.5 mg and 10 mg midazolam.

Indication: Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years).

Dose and Administration:

Age range	Dose	Label colour
3 to 6 months hospital setting*	2.5 mg	Yellow
>6 months to <1 year	2.5 mg	Yellow
1 year to <5 years	5 mg	Blue
5 years to <10 years	7.5 mg	Purple
10 years to <18 years	10 mg	Orange

*Where monitoring is possible and resuscitation equipment is available.

Treatment: BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

Parents/carers should only administer a single dose of midazolam.

The oral syringe cap should be removed before use to avoid risk of choking.

Children under 3 months: Not recommended.

Patients with renal impairment: No dose adjustment is required (see SmPC).

Patients with hepatic impairment: BUCCOLAM is contraindicated in patients with severe hepatic impairment.

Contraindications: Hypersensitivity to the active substance, to benzodiazepines or to any of the excipients, myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic impairment.

Pregnancy: The potential risk during pregnancy is unknown, however, midazolam may be used during pregnancy if clearly necessary. The risk for newborn infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Lactation: Midazolam passes in low quantities (0.6%) into breast milk and therefore it may not be necessary to stop breastfeeding following a single dose of midazolam.

Warnings and precautions: Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3–6 months age group cannot be excluded.

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function clearance of midazolam may be decreased.

Debilitated patients are more prone to the central nervous system effects of benzodiazepines and, therefore, lower doses may be required.

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

Drug Interactions: Midazolam is metabolised by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam, thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastrointestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Adverse reactions: Reported with midazolam are: Common (≥1/100 to <1/10): sedation, somnolence, depressed levels of consciousness, respiratory depression, nausea and vomiting. Uncommon (≥1/1,000 to <1/100): pruritus, rash and urticaria. Very rare (≤1/10,000) adverse reactions are listed in the SmPC.

Legal Category: POM.

Basic NHS Price:
2.5 mg: £82.00
5 mg: £85.50
7.5 mg: £89.00
10 mg: £91.50

MA Number:
2.5 mg: EU/1/11/709/001
5 mg: EU/1/11/709/002
7.5 mg: EU/1/11/709/003
10 mg: EU/1/11/709/004

Further Information from Marketing Authorisation Holder: ViroPharma SPRL, Rue Montoyer 47, 1000 Brussels, Belgium

Date of Preparation: September 2013

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 ViroPharma UK via email to uk.medinfo@viropharma.com or via ViroPharma UK Medical Information, telephone number 0800 731 2801.

Chronic Daily Headache

- with an emphasis on the medication overuse aspect of management

Prof Zaza Katsarava,
MD, PhD, MSc is a Head of the Department of Neurology at the Evangelical Hospital in Unna and a Professor of Neurology at the University of Essen in Germany. He is Board Member and Treasurer of the European Headache Federation, Chair of the Russian Linguistic Subcommitte of the International Headache Society and the Co-Chair of the Georgian National Headache Association. Dr Katsarava's main interest focuses on headache and pain, especially the risk factors and mechanisms of chronic headache.

Mark Obermann,
is Consultant Neurologist and Senior Scientist at the Department of Neurology and the German Headache Center of the University of Duisburg-Essen. As Scientific Head of the German Headache Center he has a special interested in the neurophysiologic adaptation mechanisms associated with head and facial pain in humans.

Correspondence to:
Zaza Katsarava, Prof. MD, MSc,
Chief, Department of Neurology,
Evangelic Hospital Unna,
Medical faculty, University of Duisburg-Essen
Holbeinstrasse 10, 59423 Unna,
Tel: +49 2303 106 336
Fax: +49 2303 106 134
Email: katsarava@ek-unna.de

Conflict of interest statement:
ZK has received research grants and honoraria from Allergan and Bayer, and is an advisory board member for Allergan. Headache research at the Department of Neurology in Essen was supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union.

Provenance and peer review:
Commissioned and externally reviewed

To cite:
Katsarava ZKatsarava Z, Obermann M
ACNR2013;13:6:40-42

Summary

- Purpose of review: Chronic daily headache, or "chronic headache" as now defined by the International Classification of Headache Disorders (ICHD) III, is any headache on more than 15 days per month.
- Most frequent and therefore clinically important sub-entities are chronic migraine, chronic tension-type headache and medication overuse headache (MOH).
- The current article provides a summary of the literature on the epidemiology of MOH, risk factors and treatment strategies.

The primary headaches of migraine and tension-type headache are common disorders which are associated with significant disability and economic burden. Chronic headache, defined as headache occurring on more than 15 days per month, accounts for most of the disability. In order to recognise the impact of regular use of any acute-relief medication the International Headache Society introduced the term "medication-overuse headache" (MOH).

Inappropriate use of acute-relief medication for headache may contribute to the development of chronic headache which is refractory to medical and non-drug treatments. Peters and Horton recognised this condition in the 1950s when describing chronic intractable headache in patients with migraine who used ergotamine frequently.[1,2] This was followed in the 1980s by reports of daily headache in patients, with migraine or tension-type headache, who were using analgesics or ergots on a regular basis. Importantly the chronic headache improved after discontinuation of regular acute-relief drug intake. The first International Classification of Headache Disorders (ICHD) of the IHS introduced the term 'drug-induced headache'. This was defined as a chronic headache in patients with migraine or tension-type headache following overuse of acute-relief medication (intake of analgesics or ergots on 15 days or more per month for at least 3 months) and resolving within one month of withdrawal.[3] Introduction of the triptans in the 1990s opened a new era in the treatment of migraine. Very soon it became clear that increasingly more patients used and overused triptans also. It has since been shown that triptan use on 10 days/month can lead to the development of chronic headache.[4] The second version of the ICHD introduced the term 'medication-overuse headache' (MOH) and decreased the critical threshold for triptan, ergot and opioid intake to 10 days/month. It further differentiated between MOH induced by triptans, ergots, opioids and analgesics, based upon clinical features.[5] This differentiation was widely criticised.[6] The committee of experts published appendix criteria introducing a broader concept of MOH where headache characteristics were eliminated. Moreover the definitions for chronic migraine were clarified to recognise that not all individuals improve following acute-relief drug withdrawal, but do become responsive to prophylactic medication, which had not been the case while they had been overusing.[7]

In the revised 3rd version of the ICHD three general principles have been adhered to: a) headache chronicity, b) overuse of any kind of acute-relief drugs and c) worsening of headache following overuse. The threshold for headache chronicity has been decreased from 15 days to 10 days per month. Specific MOH subgroups have been introduced: MOH following overuse of simple analgesics such as paracetamol, aspirin or other nonsteroidal analgesics, MOH due to combination drugs such as analgesics with caffeine, opioids or barbiturates, MOH due to ergots, triptans and opioids. For each of these groups the threshold of critical intake was defined between 10 and 15 days per month (personal communication, ZK is a member of the Classification Committee).

For the purpose of everyday clinical use it is essential to recognise potential MOH in patients with headache on 10 or more headache days per month with concomitant use of any kind of acute-relief drugs and treat them accordingly.

Clinical presentation

Patients with MOH are mostly women, aged 40 to 45 years. Most have migraine, but some have tension-type headache or a combination. On average they have suffered from primary headache for 20 years and overused acute-relief medication for about 5 years. Simple analgesics or combinations with caffeine are the most frequently overused drugs, followed by triptans. In the recent decade, use and overuse of ergots has decreased significantly worldwide. In Europe, very few patients overuse the combination of analgesics with barbiturates; this is much more frequent in the United States.[8,9]

Clinical features of MOH seem to depend on the pharmacology of the overused substances. Unlike migraine patients with MOH following ergot or analgesic overuse, migraine patients (but not patients with tension-type headache) who overused triptans did not develop a daily tension-type headache with

superimposed migrainous exacerbations. Instead they developed a migraine-like daily headache or, a significant increase in migraine frequency. The delay between frequent medication intake and the development of daily headache is shortest for triptans (1.7 years), longer for ergots (2.7 years), and longest for analgesics (4.8 years). Hence, triptans not only cause a different spectrum of clinical features but are also able to cause medication overuse headache faster and with lower dosages than other substance groups.[4]

Epidemiology

From epidemiological studies 1-2% of the general population suffer from chronic daily headache associated with the overuse of headache medication.[9,10]

Thanks to the efforts of the Global Campaign Against Headache and World Health Organisation (WHO), there have been several large scale population based studies addressing prevalence and burden of chronic headache in Russia, Eastern Europe, China and India.[11] Chronic headache and MOH, in particular, are an important medical and societal problem both in the developed and developing countries. The prevalence of chronic headache in developing countries is higher, e.g. 6% in Brazil[12] and 10% in Russia,[13] providing an argument against the view that headache is a problem of developed countries.

Use, and overuse, of acute-relief drugs in migraine varies between different parts of the world and depends mainly on local medical, societal and economic factors. Analgesics are most frequently used worldwide.[14] Use of triptans is more frequent in wealthy countries and fairly rare in developing countries.[22,26] Overuse of ergots has significantly decreased worldwide, especially in US and Europe.[15]

Risk factors and pathophysiology

MOH is an interaction between an excessively used acute-relief drug and a susceptible patient. The assumption of genetical susceptibility is supported by the fact that patients with migraine and tension-type headache have a higher potential for MOH than patients who use similar drugs for other diseases, such as arthritis. Patients with arthritis have a large consumption of analgesics but do not necessarily show an increased incidence of headache.[16] Patients with cluster headache usually do not develop MOH despite daily use of triptans, unless they also have a history or family history of migraine.[17]

Medication overuse is the most important risk factor and the driving force in the development of MOH. This statement seems self evident, but is difficult to confirm, because daily headache itself causes patients to use frequent painkillers. The argument for considering medication overuse as a main pathophysiological factor for headache chronicity is the fact that in the majority of cases withdrawal of the offending drug results in the improvement of headache. Furthermore, several longitudinal population-based studies have clearly demonstrated that overuse of any kind of acute-relief drugs bears a risk to developing chronic headache in the predisposed.[18] Whether some drugs bear a higher risk than the others is unclear. A recent population-based study demonstrated that regular caffeine may present a modest risk factor for the development of headache chronicity.[19] Thus caffeine combinations might also bear a higher risk for MOH. This could be compounded by a reluctance to withdraw given that caffeine withdrawal is not only associated with rebound headache but also with irritability, nervousness and restlessness.[20] A large population-based prospective study in Norway demonstrated that regular use of tranquilisers is also associated with a higher risk of MOH.[21]

Psychological co-morbidities such as depression and anxiety have been demonstrated to increase risk for MOH.[21,22] Low socioeconomic status has been identified as a further risk factor. This association has been shown in the US[23] and Europe,[24] particularly in Eastern Europe.[13]

Another important issue is the correlation between chronic headache and other body pains. Chronic headache is frequently associated with chronic back pain,[25] fibromyalgia[26] and facial pain.[27] Moreover, a bi-directional relationship between chronic headache and musculoskeletal pain has been demonstrated.[28] These findings suggest that the pathophysiology of chronification of headache and pain elsewhere in the body is likely to be interelated and to involve the entire central pain matrix.

The pathophysiology of MOH is still unknown. There is growing evidence that central sensitisation may play an important role in the pathophysiology of headache chronicity. A series of investigations using psychophysical and electrophysiological techniques demonstrated facilitation of trigeminal pain processing in patients with chronic migraine, chronic tension-type headache and MOH.[29] It is possible that each class of acute-relief drug may cause MOH via a different mechanism. Lasting changes in the serotonergic system, following exposure to painkillers, has been demonstrated in humans and animals,[30,31] while pre-treatment with opioids in rats can induce an enduring hyperalgesia, involving the peripheral and central trigeminal nociceptive system, in response to typical migraine triggers.[32]

Structural imaging studies in chronic pain, including chronic headache, have most consistently shown a decrease in grey matter volume in the pain matrix, in particular the anterior cingulate cortex [for review see 33]. An 18-FDG PET study was performed before and after acute-relief drug withdrawal.[34] Prior to withdrawal there was hypometabolism in regions of the pain matrix – bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula, ventral striatum and right inferior parietal lobule. All recovered glucose uptake following withdrawal except the orbitofrontal cortex, This occurred in patients overusing combination acute-relief preparations. In behavioural 18-FDG PET studies the abnormal activation within the striato-thalamo-orbitofrontal circuit underlies the maladaptive behaviour of substance abuse. This would be consistent with the clinical correlate that in patients who cannot maintain abstinence from overusing acute-relief drugs this is not related to severity of the disorder but behavioural, with a proportion fulfilling Diagnostic and Statistical Manual of Mental Disorders' criteria for Substance abuse disorder.[35]

From epidemiological studies 1-2% of the general population suffer from chronic daily headache associated with the overuse of headache medication

Treatment and outcome

Treatment of MOH patients should include a) education on the nature of the disorder, risk factors and treatment options, b) withdrawal, c) preventive treatment and d) multimodal approach including psychological support.[36]

Patient education is an important step in the treatment of MOH. An Akershus population based study in Norway identified people with possible MOH. A letter was provided with educational material and advice. This intervention alone resulted in improvement of headache in many cases.[37] An Italian study compared advice alone with a structured detoxification programme in patients with

MOH and without psychological co-morbidity; both arms were similarly effective.[38] The withdrawal headache usually lasts about 2-10 days and may be accompanied by a number of additional withdrawal symptoms depending on the type of acute-relief drugs overused. The withdrawal phase is much shorter for isolated triptan overuse.[39] Treatment recommendations for the acute phase of drug withdrawal has varied considerably. They include fluid replacement, rescue medication with limited amount of analgesics or triptans, tranquilisers and neuroleptics. Two independent placebo-controlled randomised studies from Norway and Germany revealed that oral prednisone (60 or 100mg per day) were not superior to placebo.[40,41]

There have been varied approaches to drug withdrawal. However the majority of patients can be withdrawn as an outpatient. Those with greater psychiatric comorbidity may need greater support and a more structured withdrawal programme.[36]

A multidisciplinary approach, involving medical, psychological and physiotherapy input has proven effective in the management of primary headaches including MOH.[42] This approach requires an initial investment in resources. Therefore, for the time being such an approach may be limited to patients with high medical needs, thus those who relapse after initial successful withdrawal and those with concomitant psychiatric co-morbidity.

Several studies have dealt with the long-term outcome of patients with MOH after successful withdrawal, defined as no headache or improvement of at least 50% in terms of headache days. The success rate over an observation period up to six months is up to about 75%. Long-term (four years) follow-up studies found relapse rates between 30-60%. Patients with migraine, rather than tension-type headache, and those who used triptans compared to other drugs had a significantly lower relapse rate.[43-45]

Conclusion

The most important measure to prevent MOH is proper general information as well as clear instruction and appropriate surveillance of patients. Migraine patients at risk often have a phenotypic mixture of migraine and tension-type headaches and should be carefully instructed to use specific antimigraine drugs for migraine attacks only. The number of doses of triptans should be limited to eight days/month based upon the work which shows that triptans used on 10 days a month can lead to the development of MOH. Drugs that contain barbiturates, caffeine, codeine, or tranquilisers, as well as mixed analgesics, should be avoided. Early and appropriate migraine prophylaxis, medical and behavioural, are important preventive measures to avoid medication-overuse headache. ◆

REFERENCES

1. Peters GA, Horton BT. *Headache: with special reference to the excessive use of ergotamine preparations and withdrawal effects.* Mayo Clin Proc 1951;26:153-61.
2. Peters GA, Horton BT. *Headache: with special reference to the excessive use of ergotamine preparations and withdrawal effects.* Mayo Clin Proc 1951;26:153-61.
3. International Headache Society. *Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.* Headache Classification Committee of the International Headache Society. Cephalalgia 1988;7 (suppl):1-96.
4. Limmroth V, Katsarava Z, Fritsche G, et al. *Features of medication overuse headache following overuse of different acute headache drugs.* Neurology 2002;59:1011-14.
5. International Headache Society. *The International Classification of Headache Disorders.* Cephalalgia 2004;24:1-160.
6. Silberstein SD, Olesen J, Bousser MG, et al. *The International Classification of Headache Disorders,* 2nd ed. (ICHD-II)-revision of criteria for 8.2 Medication-overuse headache. Cephalalgia 2005;25:460-5.
7. Olesen J, Bousser MG, Diener HC, et al. *New appendix criteria open for a broader concept of chronic migraine.* Cephalalgia 2006;26:742-6. Volltext Bibliographic Links This paper introduced the novel, broader concept of MOH.
8. Scher AI, Lipton RB, Stewart WF, et al. *Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study.* Cephalalgia 2010;30:321-8.
9. Castillo J, Munoz P, Guitera V, Pascual J. *Epidemiology of chronic daily headache in the general population.* Headache 1999;39:190-6.
10. Scher AI, Stewart WF, Liberman J, Lipton RB. *Prevalence of frequent headache in a population sample.* Headache 1998;38:497-506.
11. Steiner TJ, Birbeck GL, Jensen R, et al. *Lifting the burden: the first 7 years.* J Headache Pain 2010;11:451-5.
12. Queiroz LP, Peres MF, Kowacs F, etal. *Chronic daily headache in Brazil: a nationwide population-based study.* Cephalalgia 2008;28:1264-9.
13. Ayzenberg I, Katsarava Z; Lifting the Burden. *The prevalence of primary headache disorders in Russia: a country-wide survey.* Cephalalgia 2012;32:373-81.
14. Jonsson P, Linde M, Hensing G, et al. *Sociodemographic differences in medication use, health-care contacts and sickness absence among individuals with medication-overuse headache.* J Headache Pain 2012;13:281-90.
15. Meskunas CA, Tepper SJ, Rapoport AM, et al. *Medications associated with probable medication overuse headache reported in a tertiary care headache center over a 15-year period.* Headache 2006;46:766-72.
16. Bahra A, Walsh M, Menon S, Goadsby PJ. *Does chronic daily headache arise de novo in association with regular use of analgesics?* Headache 2003;43:179-90.
17. Paemeleire K, Bahra A, Evers S, et al. *Medication-overuse headache in patients with cluster headache.* Neurology 2006;67:109-13.
18. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. *Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study.* Headache. 2008;48:1157-68.
19. Scher AI, Stewart WF, Lipton RB. *Caffeine as a risk factor for chronic daily headache: a population-based study.* Neurology 2004;63:2022-7.
20. Silverman K, Evans SM, Strain EC, Griffiths RR. *Withdrawal syndrome after the double-blind cessation of caffeine consumption.* N Engl J Med 1992;327:1109-14.
21. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA. *Risk factors for medication-overuse headache: an 11-year follow-up study.* The Nord-Trøndelag Health Studies. Pain. 2012;153:56-61.
22. Ashina S, Serrano D, Lipton RB, Maizels M. *Depression and risk of transformation of episodic to chronic migraine.* J Headache Pain. 2012;13: 615-24.
23. Lipton RB, Stewart WF. *Migraine headaches: epidemiology and comorbidity.* Clin Neurosci 1998;9:2–9.
24. Hagen K, Vatten L, Stovner LJ, et al. *Low socio-economic status is associated with increased risk of frequent headache: a prospective study of 22718 adults in Norway.* Cephalalgia 2002;22:672-9.
25. Yoon MS, Manack A, Schramm S, et al. *Chronic Migraine and Chronic Tension-Type Headache Are Associated With Concomitant Low Back Pain: Results of the German Headache Consortium (GHC) Study.* Pain 2013 in press.
26. de Tommaso M, Sardaro M, Serpino C, et al. *Fibromyalgia comorbidity in primary headaches.* Cephalalgia 2009;29:453-64.
27. Yoon MS, Mueller D, Hansen N, et al. *Prevalence of facial pain in migraine: a population-based study.* Cephalalgia 2010;30:92-6.
28. Hagen K, Linde M, Steiner TJ, et al. *The bidirectional relationship between headache and chronic musculoskeletal complaints: an 11-year follow-up in the Nord-Trøndelag Health Study (HUNT).* Eur J Neurol. 2012;19:1447-54.
29. Ayzenberg I, Obermann M, Nyhuis P, et al. *Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures.* Cephalalgia 2006;26:1106-14.
30. Reuter U, Salomone S, Ickenstein GW, et al. *Effects of chronic sumatriptan and zolmitriptan treatment on 5-HT receptor expression and function in rats.* Cephalalgia 2004;24:398-407.
31. Srikiatkhachorn A, Anthony M. *Serotonin receptor adaptation in patients with analgesic-induced headache.* Cephalalgia 1996;16:419-22.
32. De Felice M, Porreca F. *Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache.* Cephalalgia. 2009;29:1277-84.
33. May A. *New insights into headache: an update on functional and structural imaging findings.* Nat Rev Neurol. 2009;5:199-209.
34. Fumal A, Laureys S, Di Clemente L, et al. *Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine.* Brain 2006;129:543-50. Volltext Bibliographic Links.
35. Radat, F. and Lanteri-Minet M (2010). *What is the role of dependence-related behavior in medication-overuse headache?* Headache 50(10):1597-611.
36. Evers S, Jensen R. *European Federation of Neurological Societies. Treatment of medication overuse headache--guideline of the EFNS headache panel.* Eur J Neurol 2011;18:1115-21.
37. Grande RB, Aaseth K, Benth JŠ, et al. *Reduction in medication-overuse headache after short information. The Akershus study of chronic headache.* Eur J Neurol 2011;18:129-37.
38. Rossi P, Di Lorenzo C, Faroni J, et al. *Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs.* Cephalalgia. 2006;26:1097-105.
39. Katsarava Z, Fritsche G, Muessig M, et al. *Clinical features of withdrawal headache following overuse of triptans and other headache drugs.* Neurology 2001;57:1694-8. Ovid Full Text Volltext Bibliographic Links.
40. Boe MG, Mygland A, Salvesen R. *Prednisolone does not reduce withdrawal headache: a randomized, double-blind study.* Neurology 2007;69(1):26-31.
41. Rabe K, Pageler L, Gaul C, et al. *Prednisone for the treatment of withdrawal headache in patients with medication overuse headache: A randomized, double-blind, placebo-controlled study.*
42. Zeeberg P, Olesen J, Jensen R. *Efficacy of multidisciplinary treatment in a tertiary referral headache centre.* Cephalalgia 2005;25:1159-67.
43. Diener HC, Dichgans J, Scholz E, et al. *Analgesic-induced chronic headache: long-term results of withdrawal therapy.* J Neurol 1989;236:9-14.
44. Fritsche G, Eberl A, Katsarava Z, et al. *Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse.* Eur Neurol 2001;45:229-35.
45. Katsarava Z, Muessig M, Dzagnidze A, et al. *Medication overuse headache: rates and predictors for relapse in a 4-year prospective study.* Cephalalgia 2005;25:12-15.

Echolalia; with a note on some synaesthestic phenomena

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

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

Statement of conflict of interest:
The author has indicated that there are no financial or other conflicts of interest.

Provenance and peer review:
Submitted and internally reviewed

To cite:
Larner A, ACNR2013;V13:6:43

Summary:
- The term echolalia is used by two canonical American authors: Scott Fitzgerald and Kurt Vonnegut.
- Synaesthetic phenomena may be described in Vonnegut's *Slaughterhouse-five.*
- Neurological phenomena may be described in works of literature

Echolalia

Echolalia may be defined as the involuntary automatic repetition of an interlocutor's speech.[1] The involuntary qualification excludes voluntary or wilful repetition, which many of us may have indulged in, perhaps as children, with a view to annoy or ridicule parents or friends.

There may be various clinical causes for echolalia, including autism; transcortical aphasias including dynamic aphasia; Tourette syndrome; neurodegenerative disorders such as some cases of Alzheimer's disease, behavioural variant frontotemporal dementia, and corticobasal degeneration; and focal epilepsy.

Remarkably enough, the word echolalia is used in two classics of the American 20th century literary canon.

In *The Great Gatsby* (1926) by F Scott Fitzgerald (1896-1940), at one of Gatsby's famed and opulent parties:

> There was the boom of a bass drum, and the voice of the orchestra leader rang out suddenly above the echolalia of the garden.[2]

The word seems to be used here to describe the babble or chatter of voices, and not a clinical phenomenon.

In *Slaughterhouse-five, or the Children's Crusade* (1969) by Kurt Vonnegut (1922-2007), a more extensive usage of the word echolalia appears. Billy Pilgrim, the book's protagonist, is lying in a hospital bed in 1968 having just survived an aircrash. He shares his hospital room with Professor Bertram Copeland Rumfoord of Harvard, Official Historian of the Unites States Air Force. Rumfoord is puzzling over how to incorporate in his one-volume history of the Army Air Force in World War Two an account of the bombing of the German city of Dresden on 13th February 1945 in which around 135000 civilians were killed, an event which Billy witnessed as a prisoner of war, locked in Slaughterhouse-five.

> "I was there," he said.
>
> It was difficult for Rumfoord to take Billy seriously, since Rumfoord had so long considered Billy a repulsive non-person who would be much better off dead. Now, with Billy speaking clearly and to the point, Rumfoord's ears wanted to treat the words as a foreign language that was not worth learning.
>
> "He's simply echoing the things we say ... He's got echolalia now."

The author then tells the reader that:

> Echolalia is a mental disease which makes people immediately repeat things that well people around them say. But Billy didn't really have it.
>
> Rumfoord went on insisting for several hours that Billy had echolalia – told nurses and a doctor that Billy had echolalia now.
>
> Nobody took Rumfoord's diagnosis seriously.[3]

Clearly echolalia is being used in a clinical sense here, although by a non-clinician, to label somebody as mentally deficient.

Synaesthestic phenomena

There are some other passages of possible neurological interest in Kurt Vonnegut's novel *Slaughterhouse-five*. Time is an important element in the book, indeed Billy is a traveller in time, as well as space. A passage in which time appears to run backward, such that Billy sees planes taking off backwards (i.e. appearing to land), was apparently a stimulus for Martin Amis's novel *Time's Arrow: or The Nature of the Offence* (1991). Billy is also taken to the planet Tralfamadore (alien abduction phenomenon?) where "the most important thing" he learns is that:

> All moments, past, present, and future, always have existed, always will exist.[4]

This "tenseless" philosophical viewpoint of time is picked up on by Cytowic and Eagleman in their book on synaesthesia. They discuss "number forms" or "spatial sequence synesthesia", a phenomenon reported by some synaesthetes in which number or time sequences are experienced in precise locations in relation to the body.[5]

There are some further passages in Vonnegut's novel which are perhaps suggestive of transmodal sensory experience or cross-modal activation. For example, whilst listening to the singing of a barbershop quartet on his wedding anniversary, an unexpected event occurs:

> as the quartet made slow, agonized experiments with chords ... Billy had powerful psychosomatic responses to the changing chords. His mouth filled with the taste of lemonade, and his face became grotesque, as though he .. were being stretched on .. the rack.[6]

This description includes several of the characteristics ascribed to synaesthetic experience: it was involuntary or automatic; generic or categorical ("taste of lemonade"), and affect-laden, although there is no indication as to whether the experience was consistent (how often do we hear a barbershop quartet?). In addition, during his wartime experience in Europe, Billy

> had been seeing St Elmo's fire, a sort of electronic radiance around the heads of his companions and captors. It was in the treetops and on the rooftops of Luxembourg, too, it was beautiful.[7]

This might be termed illusory visual spread or visual perseveration, other literary examples of which have been noted.[8] This might also be a synaesthetic phenomenon: Cytowic and Eagleman report a patient who "has emotionally mediated synesthesia causing him to see colored auras around objects".[9]

I do not know whether Vonnegut was synaesthetic, but it is possible he may have suffered from depressive episodes and post-traumatic stress disorder, perhaps related to his war experience in Dresden.[10] ◆

REFERENCES

1. Larner AJ. *A dictionary of neurological signs (3rd edition).* London: Springer, 2011:125-6.
2. Fitzgerald FS. *The Great Gatsby.* London: Penguin, 1990 [1926]:50.
3. Vonnegut K. *Slaughterhouse-five, or the Children's Crusade.* London: Vintage, 2000 [1969]:140-1.
4. Ibid.:19.
5. Cytowic RE, Eagleman DM. *Wednesday is indigo blue. Discovering the brain of synesthesia.* Cambridge: MIT Press, 2009:124-5.
6. Op. cit., ref. 3:125-6.
7. Op. cit., ref. 3:46.
8. Larner AJ. *Illusory visual spread or visuospatial perseveration.* Adv Clin Neurosci Rehabil 2009;9(5):14.
9. Op. cit., ref. 5:10.
10. Shields CJ. *And so it goes: Kurt Vonnegut, a life.* New York: Henry Holt, 2011.

Copaxone

- Helping RRMS patients maintain a working life[1]
- As effective as IFN beta-1a s.c.(44mcg) at reducing relapses[2]

COPAXONE®
(glatiramer acetate)
Standing up to RRMS every day

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

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 Teva UK Limited on 0207 540 7117 or medinfo@tevauk.com

References
1. Ziemssen T et al. *Health Qual Life Outcomes* 2008; 6:67.
2. Mikol DD et al. *Lancet Neurology* 2008; 7:903-914.

Teva UK Limited
Riding Point,
Whistler Drive,
Castleford,
West Yorkshire WF10 5HX

TEVA UK Teva UK Limited

UK/CPX/13/0009 July 2013