ISSN 1473-9348 VOLUME 14 ISSUE 6 JANUARY/FEBRUARY 2015

ACNR

www.acnr.co.uk

ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

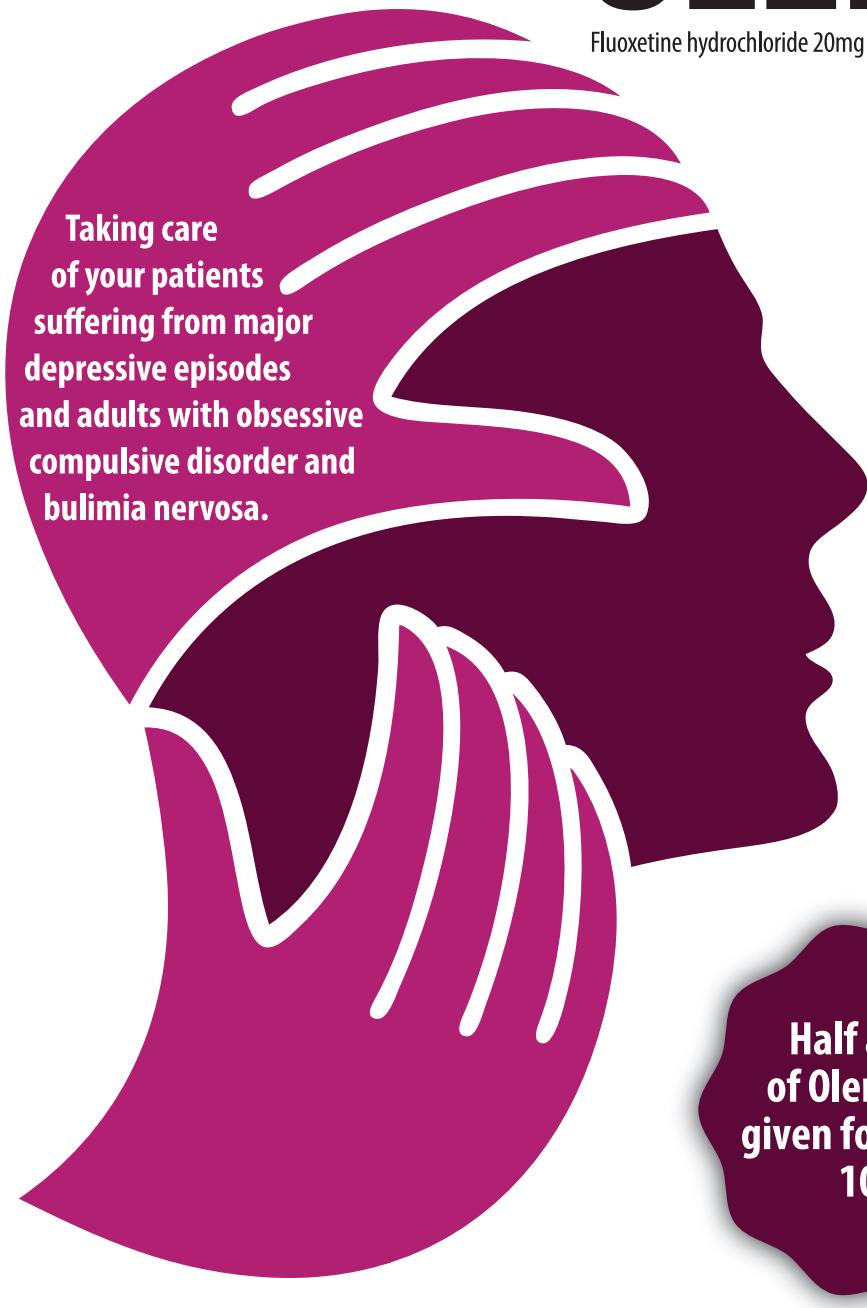
OLENA

Fluoxetine hydrochloride 20mg Dispersible Tablets

The first and only dispersible fluoxetine tablet in the UK.

An option to help aid compliance in patients with difficulty in swallowing tablets

A cost effective alternative to fluoxetine 20mg/5ml syrup.[1]



Half a tablet of Olena can be given for a dose of 10mg.

AMCo
Amdipharm Mercury

PRESCRIBING INFORMATION: Olena 20mg Dispersible Tablets Fluoxetine hydrochloride. **Presentation:** Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20mg fluoxetine. **Indications:** *Adults:* Major depressive episodes, obsessive-compulsive disorder and bulimia nervosa. *Children and adolescents aged 8 years and above:* Moderate to severe major depressive episode. **Dosage and administration:** For oral administration. *Adults and Elderly:* The recommended dose is 20mg daily which may be increased gradually to a maximum of 60mg. Caution is recommended when increasing the dose in elderly. *Children:* The starting dose is 10mg/day given as half of a tablet. Abrupt discontinuation should be avoided and the dose should be gradually reduced. **Contraindications:** Hypersensitivity to any of the components. Combination of fluoxetine with MAOIs. **Precautions and warnings:** Caution should be exercised when used in children and adolescents under 18 years of age, seizures, mania. Lower dose is recommended in patients with hepatic dysfunction. Patients with cardiovascular effects, fructose intolerance and patients taking St. John's wort should be cautious. An adjustment of dose is recommended in patients experiencing weight loss, diabetes, suicide/suicidal thoughts, haemorrhage and mydriasis. **Interactions:** Serotonergic drugs, phenytoin, lithium, tryptophan, CYP2D6 isoenzymes, oral anticoagulants, alcohol and other SSRIs. **Pregnancy and lactation:** Fluoxetine can be used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour. Increased risk of cardiovascular defects when used in first trimester. It is known to be excreted in human breast milk. **Undesirable effects:** *Common:* Headache, nausea, insomnia, fatigue, diarrhoea, anxiety, nervousness, restlessness, tension, libido decreased, sleep disorder, abnormal dreams, disturbance in attention, dizziness, lethargy, somnolence, tremor, vomiting, dyspepsia, dry mouth, palpitation, QT prolongation, cardiac arrhythmias, flushing and blurred vision, oesophageal pain, hypotension and increased risk of bone fractures in patients receiving SSRIs and TCAs. (Please refer Summary of Product Characteristics for detailed information). **Overdose:** Symptoms of overdose include nausea, vomiting, seizures, cardiovascular dysfunction and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. **Legal category:** POM. **Basic NHS cost:** £3.44 for 28 x 20mg.

Marketing authorisation Number: PL 12762/0475. **Marketing Authorisation Holder:** Amdipharm Mercury Company Limited (AMCo), 1st Floor, Capital House, 85 King William Street, London, EC4N 7BL. **Date of preparation:** October 2013. **Date of revision:** December 2013.

Ref 1: NHS electronic Drug Tariff, NHS business service authority. Part VIIIA products F.[online]. [Accessed on 03/12/13]. Available at http://ppa.org.uk/edt/December2013/mindex.htm

Adverse events should be reported to the local regulatory authority. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Amdipharm Mercury Medical Information via telephone on 08700 70 30 33 or via e-mail at medicalinformation@amcolimited.com.

UK/OLE/AD/105B/2014 Date of preparation: June 2014

CONTENTS

JANUARY/FEBRUARY 2015

ACNR

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

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

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

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

PRINTED BY Warners Midland PLC T. 01778 391000

Editorial board and contributors

Mike Zandi, Editor.

With the NHS already saturating the newspaper front pages in the first few days of 2015, the provision and commissioning of acute neurology deserves to be at the forefront of our UK readers' concerns. Professor Kevin Talbot introduces us to the Association of British Neurologists Acute Neurology Report and Quality Standards on page 19.

In our Stroke review article, Aine Merwick and Peter Kelly from London and Dublin provide a helpful review on the prediction of stroke after transient ischaemic attack. The authors dissect clinical and imaging predictors, discussing the uses and misuses of the ABCD2 tool and the newer ABCD3-I tool. David Werring introduces this article on page 8, and we are pleased that David will stay on as Stroke Editor for the journal, continuing the emphasis on Stroke beyond the current strong series of articles. In their review article, Ed Newman and Peter Kennedy from Glasgow provide an update on structural and functional imaging changes in multiple system atrophy, progressive supranuclear palsy, dementia with Lewy Bodies and corticobasal degeneration.

Tom Foltynie (UCL) explores the link between LRRK2 and axonal transport in the journal reviews section, with Kevin Talbot (Oxford) reviewing one of the year's most definitive papers on the pathogenic mechanism of C9ORF72 by the group of Adrian Isaacs (UCL). Mark Manford reviews the December American Epilepsy Society meeting amongst our conference reviews. We are pleased to publish a personal perspective from Diana Mann, who recounts her experience of and recovery from meningococcal septicaemia and subsequent epilepsy, and also a Neurologist's career perspective (Chris Allen). Romi Saha (Hurstwood Park), Paul Worth (Addenbrooke's) and Jon Stamford (Parkinson's Movement and Scientific & Advocate Communication Coordinator for the Cure Parkinson's Trust) write in a special feature on measuring quality of life in Parkinson's disease in routine clinical settings, and highlight that 31% of patients in one survey still feel their priorities are sometimes or rarely listened to in consultations. We hope you enjoy ACNR into 2015 and welcome your suggestions for the journal.

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

Imaging and atypical parkinsonism

EJ Newman

Dr Ed Newman is a Consultant Neurologist working at Glasgow Royal Infirmary and the Institute of Neurological Sciences, Southern General Hospital. He runs the undergraduate clinical neurology teaching for University of Glasgow and has a clinical interest in movement disorders.

PGE Kennedy

Professor Peter GE Kennedy CBE is the Burton Chair of Neurology in the University of Glasgow and Consultant Neurologist in the Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland.

Correspondence address:
EJ Newman,
Institute of Neurological Sciences,
Southern General Hospital, Glasgow

Conflict of interest statement:
Neither author has any conflict of interests to declare.

Provenance and peer review:
Commissioned and peer reviewed.

To cite:
Newman EJ, Kennedy PGE.
ACNR 2015;14(6):5-7.

Introduction

The spectrum of parkinsonian syndromes is wide and, due to the lack of specific biomarkers, their diagnosis remains largely clinical. Disorders that are most commonly referred to as 'atypical parkinsonism' comprise progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB).The characteristic features of these disorders are well recognised. However, these features may be absent or ambiguous at initial diagnosis and the clinician may be uncertain about the L-dopa response. Many atypical parkinsonism cases initially resemble idiopathic Parkinson's disease (PD).

Furthermore, clinicopathological studies have suggested varying and overlapping phenotypes between these disorders. Early diagnostic accuracy is not only important for patients and their families, particularly with respect to prognosis, but also imperative for researchers entering patients into clinical studies. Identification of patients in the pre-symptomatic phase is also essential for evaluation of potential disease modifying agents. There has been much discussion regarding abnormal imaging findings in atypical parkinsonism, but the question arises as to how useful these are in clinical practice .In this brief article we will outline how structural and functional imaging can aid the diagnosis of atypical parkinsonism.

Part 1: Atypical parkinsonism

PSP:

Pathologically PSP is characterised by neuronal loss, gliosis and the presence of microtubule-associated tau inclusions within neuronal and glial cells. A genome-wide association study in PSP has recently identified new loci potentially related to underlying disease pathogenesis.[1] There are two main clinical subtypes: Richardson syndrome (PSP-R) and PSP-parkinsonism (PSP-P), which appear to differ pathologically as well as clinically. PSP-R is the classic phenotype: patients present with falls, executive dysfunction, eye movement abnormalities (initially with slowed saccades and evolving into supranuclear gaze palsy), dysarthria and marked postural instability. In PSP-P there is bradykinesia, limb and axial rigidity, and sometimes a jerky tremor at presentation. Signs may be asymmetric and initially be L-dopa responsive. Rarer subtypes include PSP-pure akinesia with gait freezing, PSP-corticobasal syndrome and PSP-frontotemporal dementia. The Movement Disorder Society Task Force is currently reviewing the diagnostic criteria for PSP and these should be published in 2015.

MSA:

There are two main clinical subtypes of MSA: MSA with parkinsonism (MSA-P) and MSA with cerebellar signs (MSA-C), with progressive autonomic failure and falls being common to both. MSA-P may be difficult to differentiate clinically from PD although the former's signs are usually more symmetrical. MSA-C patients present with gait ataxia, dysarthria, cerebellar and oculomotor dysfunction, often with little evidence of parkinsonism. Other features may include stridor and pyramidal signs. MSA is generally poorly L-dopa responsive and a minority of patients have cognitive dysfunction.[2]

In common with PD and DLB, pathologically MSA is an alpha-synucleinopathy, except that oligodendroglia rather than neurones are affected. Although these lesions are widespread they are predominantly located within olivopontocerebellar regions in MSA-C and within striatonigral regions in MSA-P.[3] Furthermore, the burden of these inclusions is greater with increasing disease duration and severity. Familial MSA is very rare, but variants in the alpha-synuclein gene have been associated with an increased disease risk.[4]

CBD:

CBD is possibly the most challenging atypical parkinsonism to diagnose accurately. The classic presentation is with a corticobasal syndrome (CBS) consisting of asymmetric akinetic-rigid parkinsonism, ideomotor apraxia, dystonia, myoclonus and the alien limb phenomenon. However, post-mortem studies have shown that only 50% of CBS patients clinically diagnosed during life pathologically had CBD, with other causes of CBS including PSP, Alzheimer's disease and frontotemporal dementia (FTD). Furthermore, rarer CBD phenotypes include FTD, progressive non-fluent aphasia and Richardson syndrome. The clinical diagnostic criteria for CBD were updated in 2013 and cases can be divided into probable and possible.[5] Pathologically there are tau-positive inclusions with cortical and striatal neuronal and glial cells with marked neuronal cell loss in frontoparietal and nigral regions.

DLB:

Like PD and MSA, DLB is an alpha-synucleinopathy. Parkinson's disease dementia and DLB are pathologically considered as a continuum with little change in the distribution or quantity of Lewy bodies and neurites. Clinically DLB is differentiated by the predominance of dementia at presentation or within 12 months of motor symptoms.[6] In DLB the cognitive impairment is characterised by deficits in

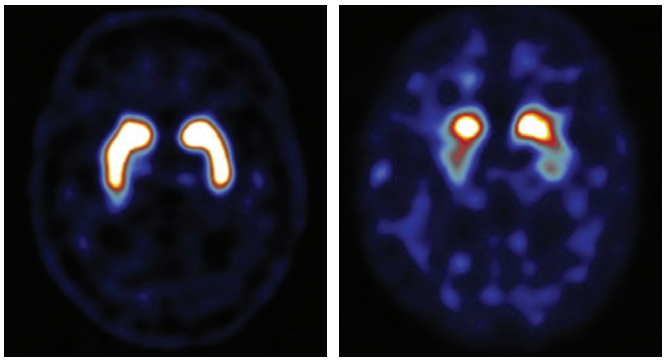


Figure 1 – The FPCIT SPECT image on the left demonstrates normal striatal function. The image on the right demonstrates markedly reduced dopaminergic function with radioligand uptake confined to the caudate in a patient with progressive supranuclear atrophy.

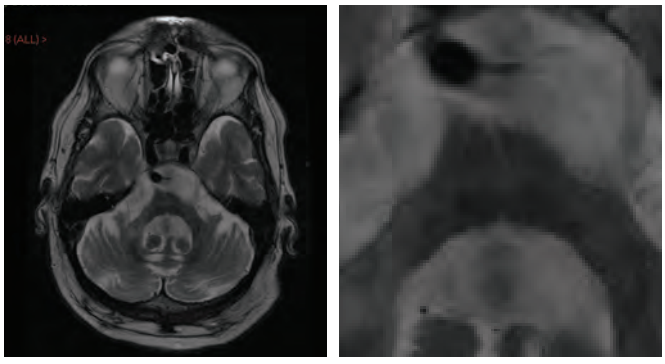


Figure 2 – These MRI images demonstrate marked pontine and cerebellar atrophy in a patient with cerebellar variant of multiple systems atrophy. The 'hot cross bun sign' can be seen on the right image.

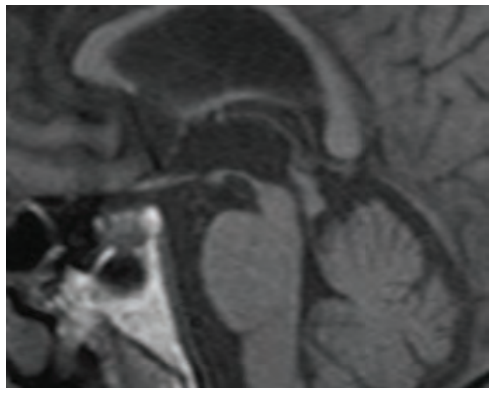


Figure 3 – Hummingbird sign illustrating midbrain atrophy in progressive supranuclear palsy.

attention and executive function. Other features include fluctuations of cognition, visual hallucinations and sensitivity to neuroleptic and anticholinergic medication.

Part 2: Structural imaging

In the past, patients with dopa-unresponsive parkinsonism were investigated with conventional structural brain imaging to identify cases of cerebrovascular disease and also exclude rare causes of parkinsonism such as hydrocephalus. More recently MRI has become a helpful adjunct in the differentiation of the atypical parkinsonian syndromes. While the specificity of the abnormal signs described may be high their sensitivity in early disease, particularly using a 1.5 Tesla scanner, is less impressive. Nevertheless, they can all serve as pointers towards the diagnosis in uncertain cases.

PSP

Atrophy of the mid-brain, superior cerebellar peduncle, frontal and parietal lobes, and dilatation of the 3rd ventricle have all been reported in PSP. Signs of midbrain atrophy have been variously described as the 'morning glory flower sign' (concavity of the lateral midbrain tegmentum on axial scans), or the 'hummingbird' or 'penguin-silhouette sign' (where the shape of the midbrain tegmentum represents the bird's head and the pons represents its body on mid-sagittal sequences). Various advanced MRI techniques such as magnetic resonance volumetry (MRV) and voxel-based morphometry (VBM), diffusion-tensor imaging (DTI), magnetic resonance spectroscopy (MRS) have been used to study PSP in a research setting. However, a recent study of pathologically confirmed PSP, MSA and PD cases reported that a simple mid-sagittal midbrain measurement of <9.35mm and a ratio of midbrain to pons of <0.52 on conventional MRI had 100% specificity for PSP.[7]

MSA

In MSA atrophy is most evident in patients with well-established disease. Structural imaging changes recognised in MSA-P include high T2-weighted signal within the posterolateral putamen, reflecting gliosis and iron deposition.[8] In MSA-C the atrophy is infratentorial affecting the pons, middle cerebellar peduncle and cerebellum. Axial T2-weighted images can reveal a cross in the pons, reflecting disruption of transverse pontocerebellar tracts, and is known as the 'hot cross bun' sign. Whilst this is usually associated with MSA-C, it has also been recognised in other neurodegenerative disorders (including spinocerebellar ataxia types 2 and 3).

CBD and DLB

Asymmetric frontoparietal atrophy can be seen with CBD. Usually the lack of midbrain atrophy helps to differentiate this from similar patterns of atrophy seen in PSP. There may be generalised cortical atrophy in DLB but the most useful finding is often preservation of medial temporal structures, which helps in differentiation from Alzheimer's disease.

Part 3: Functional imaging

Over the past 15 years functional imaging has established a role in the differentiation of PD from non-degenerative disorders.[9] Non-degenerative disorders clinically mistaken for PD include essential tremor, dystonic tremor, and drug-induced, vascular or psychogenic parkinsonism.

^{18}F dopa PET indirectly measures nigrostriatal function and is abnormal in degenerative parkinsonism. However, it is dopamine transporter (DaT) SPECT scanning that has become widely available and utilised in Europe. DaT is a sodium chloride-dependent transmembrane protein located on the presynaptic cell surface. The most commonly used DaT-binding radioligand is FPCIT.

By the time patients present with motor features of PD they have lost up to 80% of their dopaminergic neurones. Consequently DaT SPECT is abnormal at diagnosis, and in the pre-motor phase. Furthermore, visual assessment techniques are equally reliable as semi-quantitative measures in FPCIT SPECT making the interpretation technically easier.

DaT SPECT is also abnormal in atypical parkinsonism, notably PSP, MSA and DLB. It has been suggested that patterns of abnormal radioligand uptake differ between types of degenerative parkinsonism. For example, in PD there is reduced uptake in the putamen before the caudate is affected, whereas in PSP there can be uniform striatal involvement at presentation. However, it remains impossible to reliably differentiate between PD, PSP and MSA using DaT SPECT alone.[10]

DaT SPECT is abnormal in DLB but does not distinguish it from PD dementia. It is slightly less useful in CBD with 10% of patients having normal scans.[11]

Imaging of the post-synaptic D2 receptors with IBZM SPECT has also been studied in combination with DaT SPECT in atypical parkinsonism. IBZM SPECT is often abnormal in MSA and PSP, but tends to be normal in CBD and DLB. If abnormal, it carries a high positive predicative value but it does not differentiate between MSA and PSP and has been used less frequently in recent years.

Part 4: Other techniques

In PD transcranial sonography (TS) reveals hyperechogenicity of the substantia nigra and has a positive predictive value of 93%.[12] Its clear advantage is that it is non-invasive and cheap, but it requires an adequate

temporal bone window. Furthermore, 10% of the population have abnormal susbstantia nigra echogenicity. In MSA a combination of striatal hyperechogenicity and normal echogenicity of the substantia nigra can distinguish MSA-P from PD.[13] TS is also abnormal in PSP and CBD.

Another imaging method that has been studied in atypical parkinsonism is MIBG myocardial scintigraphy. This is usually reduced in PD and normal or slightly low in MSA-C.[14] However, this technique has largely remained a research tool.

Conclusions

The importance of early and accurate diagnosis in neurodegenerative disorders cannot be overstated. The spectrum of atypical parkinsonian disorder is wide and until such time as reliable biomarkers are identified these disorders will continue to be diagnosed on clinical grounds. The challenge is greatest in early disease when characteristic clinical features may be subtle, if present at all. The recognised changes on structural imaging may not be present in these early stages but can certainly inform the diagnostic process in individual cases. Functional dopaminergic imaging also has a role, and has the advantage of being abnormal at an earlier clinical stage, but does not allow reliable differentiation between disorders. ◆

REFERENCES

1. Höglinger GU, Melhem NM, Dickson DW, Sleiman PMA, Wang L-S, Klei L, et al. *Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy.* Nat Genet. 2011 Jul;43(7):699–705.
2. O'Sullivan SS, Massey LA, Williams DR, Silveira-Moriyama L, Kempster PA, Holton JL, et al. *Clinical outcomes of progressive supranuclear palsy and multiple system atrophy.* Brain. Oxford University Press; 2008 May;131(Pt 5):1362–72.
3. McCann H, Stevens CH, Cartwright H, Halliday GM. *Parkinsonism and Related Disorders.* Parkinsonism and Related Disorders. Elsevier Ltd; 2014 Jul 20;20(S1):S62–7.
4. Ahmed Z, Asi YT, Sailer A, Lees AJ, Houlden H, Revesz T, et al. *The neuropathology, pathophysiology and genetics of multiple system atrophy.* Neuropathol Appl Neurobiol. Blackwell Publishing Ltd; 2012 Feb;38(1):4–24.
5. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. *Criteria for the diagnosis of corticobasal degeneration.* Neurology. Lippincott Williams & Wilkins; 2013 Jan 29;80(5):496–503.
6. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. *Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.* Neurology. Lippincott Williams & Wilkins; 2005. pp. 1863–72.
7. Massey LA, Jäger HR, Paviour DC, O'Sullivan SS, Ling H, Williams DR, et al. *The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy.* Neurology. Lippincott Williams & Wilkins; 2013 May 14;80(20):1856–61.
8. Schrag A, Good CD, Miszkiel K, Morris HR, Mathias CJ, Lees AJ, et al. *Differentiation of atypical parkinsonian syndromes with routine MRI.* Neurology. 2000 Feb 8;54(3):697–702.
9. Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, et al. *Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group.* Mov Disord. 2000 May;15(3):503–10.
10. Booth TC, Nathan M, Waldman AD, Quigley AM, Schapira AH, Buscombe J. *The Role of Functional Dopamine-Transporter SPECT Imaging in Parkinsonian Syndromes, Part 2.* AJNR Am J Neuroradiol. American Society of Neuroradiology; 2014 Jun 12.
11. Cilia R, Rossi C, Frosini D, Volterrani D, Siri C, Pagni C, et al. *Dopamine Transporter SPECT Imaging in Corticobasal Syndrome.* Dawson TM, editor. PLoS ONE. Public Library of Science; 2011;6(5):e18301.
12. Gaenslen A, Unmuth B, Godau J, Liepelt I, Di Santo A, Schweitzer KJ, et al. *The specificity and sensitivity of transcranial ultrasound in the differential diagnosis of Parkinson's disease: a prospective blinded study.* Lancet Neurol. 2008 May;7(5):417–24.
13. Berg D, Godau J, Walter U. *Transcranial sonography in movement disorders.* Lancet Neurol. 2008 Nov;7(11):1044–55.
14. Chung EJ, Lee WY, Yoon WT, Kim BJ, Lee GH. *MIBG scintigraphy for differentiating Parkinson's disease with autonomic dysfunction from Parkinsonism-predominant multiple system atrophy.* Mov Disord. Wiley Subscription Services, Inc., A Wiley Company; 2009 Aug 15;24(11):1650–5.

Founder of Matthew's Friends charity awarded MBE

Emma Williams, Founder/CEO of Matthew's Friends and Mum of Matthew, has been awarded an MBE for her services to Children with Epilepsy.

Julie Edwards, Trustee of the charity says "No-one is more deserving than Emma for her selfless and tireless work over the years and her continued drive and remarkable determination to help those who live with drug-resistant epilepsy. Emma's passion and championing of Ketogenic Dietary Therapies has made a huge difference to so many affected families and her work nationally and internationally has impacted enormously on the positive awareness of these treatments. Achieving this whilst caring for her own severely disabled son Matthew and his sister Alice is truly inspirational to us all."

UKABIF Award for inspiration

Professor Nick Alderman, Director of Clinical Services, Brain Injury Services, has won the UK Acquired Brain Injury Forum (UKABIF) Stephen McAleese Award for inspiration by an individual in the field of acquired brain injury.

UKABIF Award winners were announced on 27th November in London at the organisation's sixth annual conference.

Announcing the award, Professor Michael Barnes, UKABIF Chair said "Nick has made an outstanding contribution to neurorehabilitation and he's a well-deserved winner of this Award".

Chartered Psychologist and Chartered Scientist, Prof Alderman was selected for successfully reducing the need for restrictive intervention in managing recovery, through his development of observational rating scales and outcome measures now accepted as the best available, including tools called OAS-MNR, SASBA and SASNOS. He also co-authored BADS, a widely used test of executive functioning capabilities. He has also been instrumental in developing clinical interventions to reduce social handicap associated with neurobehavioural disability.

On receiving the award from John and Susan McAleese, parents of Stephen McAleese, Professor Alderman said "Stephen McAleese dedicated his life to raising awareness of acquired brain injury and to helping others; he was a truly inspirational individual. I feel honoured and humbled to be the recipient of this award from UKABIF which bears his name."

Introduction to the ACNR Stroke Series

A key aspect of the revolution in the approach to stroke medicine in recent years has been increased awareness of the very high early risk of ischaemic stroke after TIA, with realisation that a TIA syndrome is thus a unique and golden opportunity to avert future disaster by early investigation and treatment. As part of this revolution, risk scores have been developed and widely enshrined in national guidelines and stroke care pathways, especially the ABCD2 score. Such scores may have a very useful role in patient triage, but are subject to misunderstanding of their intended purpose (e.g they are not diagnostic instruments), and to misuse in clinical practice. In this next article in the Stroke series, Aine Merwick and Peter Kelly give an excellent clear and comprehensive insight into the development and implementation of TIA risk prediction scores, with elegant explanation of the statistical approaches needed, as well as a summary of their limitations and a look to the future of such instruments.

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

Predicting ischaemic stroke risk after TIA: promise and pitfalls

Summary

- Stroke risk following TIA is highest in the days immediately following a TIA.
- Risk prediction tools can identify patients at low and high risk of stroke in the short term following TIA.
- Urgent brain and vessel imaging improves risk prediction following TIA.
- External validation and cost effectiveness studies of clinical prediction tools such as the ABCD3-I may help demonstrate their utility in everyday clinical practice.

Introduction

Transient ischaemic attack (TIA) is associated with high risk of early stroke, with stroke rates of 10-13% reported in population studies with routine treatment.[1] Early recognition and treatment of TIA provides an ideal opportunity for rapid intervention to prevent stroke and related sequalae. TIA is also an important marker of risk of late stroke recurrence, coronary events and cognitive impairment.[2,3,4] When combined with clinical assessment by a trained physician, clinical prediction scores for stroke risk after TIA have the potential to be valuable aids, particularly for identification of patients at highest stroke risk.

In practice identifying which patient may be most high risk is a challenge, and therefore clinical prediction tools can be helpful for answering patient's questions regarding likelihood of stroke after a TIA.

Clinical prediction tools and ABCD2 score

The ideal characteristics of a predictive score include transportability (also termed generalisability and demonstrated by external validation), good calibration (defined as comparison of observed and predicted event rates for groups of patients) and discrimination (the ability of the risk prediction models to distinguish those who go on to experience an outcome event from those who do not).[5,6,7]

Epidemiological studies have shown that older age, hypertension, diabetes mellitus, and multiple recent TIAs are associated with stroke risk.[1,8] Further clinical features including motor weakness, speech disturbance, and symptom duration ≥ 60minutes were associated with increased stroke risk.[1,8,9]

Based on the features identified in studies of stroke risk following TIA, a simple clinical prediction tool was devised for triage purposes. The ABCD2 clinical prediction score was originally intended for use at the initial evaluation of patients with suspected TIA by primary care and emergency department physicians to aid triage decisions for hospital admission and urgent referral to specialist stroke services.[9] The ABCD2 score (age ≥60 years [1 point]; blood pressure ≥140/90mmHg [1 point]; clinical features of weakness [2 points] or speech impairment [1 point]; duration of symptoms ≥60 min [2 points] or 10-59 min [1 point]; diabetes mellitus [1 point]) has been developed based on information obtained on basic clinical examination and history taking.[9] The score was deliberately designed not to include information frequently obtained after initial investigations have been performed, as it was designed for use by general practioners and emergency department doctors. The score was designed with the aim of helping to accurately triage patients and specifically to identify which patients may be managed in an outpatient/clinic setting (low risk patients) and identify high risk patients, who may benefit most from hospitalisation and/or prioritised diagnostic investigations and treatments.[9] Ideally prediction scores for TIA patients would have high sensitivity

Aine Merwick, MB, MSc (Stroke), PhD
has completed her specialist training in neurology and is an Honorary Clinical Neurologist and Research Associate at the National Hospital for Neurology and Neurosurgery, Queen Square, London. She has special interest in TIA and risk prediction, as well as large vessel disease and neuro-metabolic medicine.

Peter J Kelly
is a Consultant Neurologist and Director of Stroke Service at, Mater University Hospital Dublin and Neurovascular Unit for Translational Research and Therapeutics, UCD/DAMC Catherine McAuley Centre Dublin. He spent seven years at Massachusetts General Hospital and worked at Harvard School of Public Health before returning to Dublin. His academic work is focused on stroke prevention and translational research aimed at developing new surrogate markers for early clinical trials of stroke treatments. He is the Principal Investigator of several ongoing studies of stroke and is a Professor of Neurology at University College Dublin.

Correspondence to:
Professor Peter Kelly
Neurovascular Clinical Science Unit
Catherine McAuley Research Centre
Nelson Street
Mater University Hospital
Dublin 7, Ireland.
Tel: +353 (0)1-7166374
Fax: +353 (0)1-7166357
Email: ndpss@mater.ie

Conflict of interest statement:
Prof Kelly is funded by a Clinician Scientist Award from the Health Research Board of Ireland, and by the Irish Heart Foundation. Dr Merwick has received salary funding from the Health Service Executive (HSE) Ireland/Dr Richard Steeven's scholarship and Ainsworth Prize from University College Cork

Provenance and peer review:
Commissioned and internally reviewed.

To cite:
Merwick A, Kelly P.
ACNR 2015;14(6):8-11.
Published online first: 3 December, 2014

and high specificity. To determine the validity of a predication score, its discriminative ability to predict stroke is usually evaluated by receiver-operating characteristic (ROC) analysis and the c-statistic (corresponding to area under the ROC curve) calculated. Ideal discrimination produces a c-statistic of 1.0 whereas discrimination which is no better than chance produces a c-statistic of 0.5.[6,7]

In the original ABCD2 score derivation study the clinically based score predicted stroke by two days after TIA (c-statistic 0.62-0.79) and by seven days after TIA (c-statistic 0.63-0.83).[9] Based on clinical outcome events risk categories were assigned (0-3 low risk, 4-5 moderate risk, 6-7 high risk).[9] Current international guidelines for use of the ABCD2 prediction tool, have mostly adopted either a greater than or equal to 4 threshold.[10,11]

External validity of the ABCD2 score has been demonstrated in a meta-analysis of 11 independent TIA cohorts (ie. excluding the original samples in which the score was derived and validated). On receiver operating characteristic analysis, the pooled area-under-curve (AUC) for seven day stroke was 0.69 (CI 0.64-0.74).[12]

Carotid stenosis, neurovascular imaging and risk prediction after TIA

Imaging evidence of carotid stenosis (≥50% lumen narrowing) has also been linked with high risk of early recurrence in several studies. In a population based study of 433 TIA patients the hazard ratio (HR) of 90-day stroke recurrence associated with any carotid stenosis >50% was 2.6 (95% CI, 1.28 to 5.20) and with >70% carotid stenosis was 3.3 (95% CI, 1.5 to 7.4, P=0.002).[13] The risk of 90-day stroke was seen to rise in a linear fashion with increasing severity of carotid stenosis, ranging from 5.4% (<50% stenosis) to 17.2% (>70% stenosis or occlusion) (P=0.002). Carotid stenosis had moderate sensitivity (43.8%) but high specificity (77.9%) for identification of TIA patients who subsequently developed 90-day stroke. In the OXVASC study patients with posterior circulation TIA, 50% vertebral and basilar stenosis was also associated with 90-day risk of recurrent stroke/TIA (OR 3.2, P=0.006), with rates of 22% for stroke and 46% for TIA or stroke recurrence.[14]

Several groups have demonstrated that addition of brain imaging, especially magnetic resonance imaging (MRI) data may enhance the predictive utility of existing clinical scores.[15-18] Diffusion weighted imaging sequences are sensitive to detecting ischaemic changes after TIA (Figure 1). Coutts and colleagues devised an ABCD2 + MRI scoring system in which the ABCD2 score items were retained and two MRI items added (presence of a DWI lesion (1 point) and intracranial vessel occlusion (1 point)). The combined score predicted 90-day recurrent stroke better than ABCD2 (AUC of 0.88 versus 0.78, P=0.01).[15] Giles and colleagues conducted a meta-analysis in 4,574 patients imaged with either brain CT or MRI.[18] The presence of infarction on DWI was a more powerful predictor of stroke, than ischaemic change on CT. The odds ratio (OR) for stroke with brain infarction on DWI was 14.9 (7.4-30.2) and on CT was 4.2 (2.6-6.9).[18]

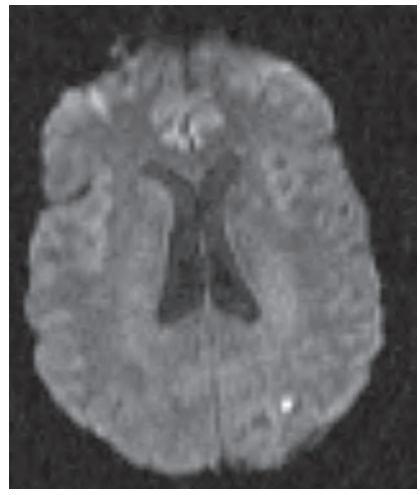


Figure 1: DWI image showing acutely restricted diffusion in left parietal lobe in a 45-year-old patient who presented with a TIA.

An ideal risk prediction score when compared to an existing score has improved net reclassification (defined as the difference in proportions moving up to a higher score value and down to a lower score value, from one score when compared to another score), and high inter user reliability (low variation in measurements when taken by different users, and high consistency to scoring).[7] Furthermore, an ideal clinical prediction score has applicability across different health care settings, clinical credibility and effectiveness (how well a score works in clinical practice) and is straightforward to use in clinical practice.[5,6,7]

In a pooled analysis of individual patient data from 2,654 TIA patients, a refined clinical and imaging-based prediction score was derived by logistic regression modelling (ABCD3-I) with two points assigned each for 'dual TIA' (defined as an earlier TIA within seven days of the TIA prompting medical assessment), positive DWI, and stenosis >50% on carotid imaging.[19] The 13-point ABCD3-I score substantially improved predictive ability compared to the ABCD2 score. The ABCD3-I score improved predictive and risk classification of TIA patients with and without stroke (90-day net reclassification improvement 39.4%, p=0.034).[19] When the ABCD3-I score was applied in an independent validation sample of 1,232 patients from two population-based studies, the c-statistic increased at each time interval compared to the ABCD2 score (from 0·63 to 0·71 [p=0·045] at seven days; from 0·60 to 0·71, p=0·007 at 90 days).[19]

The ABCD3-I score has been further independently externally validated in five separate cohorts to date.[20-24] In a German single centre hospital based study of 235 patients the score was associated with early in hospital stroke recurrences (p=0.021).[20] In a Chinese study of 107 patients the AUC for seven day stroke prediction was 0.74, with a further study among 239 eligible patients, showed an AUC of ABCD3-I scores (0.825; 95% confidence interval, 0.752–0.898) was statistically higher than that of ABCD2 scores (0.694; 95% confidence interval, 0.601–0.786; P<0.001).[21,22] In a large multi-centre Spanish study the ABCD3-I score was shown to be a powerful predictor of subsequent stroke with an AUC of 0.83 (95% CI 0.72-0.93) at seven days and 0.69 (95% CI 0.53-0.85) at 90 days.[23] Improvement in risk classification by the ABCD3-I score when compared to the ABCD2 score has also been shown in a Japanese population.[24]

The ABCD3-I score is simple to apply, has been independently externally validated, and has the potential to improve risk stratification after TIA in secondary care settings.

Potential for enhanced risk prediction in TIA patients

Several techniques may have a future role in TIA risk prediction. Lipoprotein-associated phospholipase A2 (LPPLA2), a serum marker of plaque macrophage activation was independently associated with a combined outcome measure of stroke, death, large artery or cardioembolic mechanism in 147 acute TIA patients.[25] Other substances have also been suggested as biomarkers for stroke risk prediction but validation and determination of the utility of serum biomarkers remains to be verified.

Combining follow-up imaging after TIA with novel imaging modalities such as perfusion weighted imaging (PWI), or arterial spin label imaging may help better characterise stroke risk.[26,27]

Stroke prediction in patients with carotid stenosis is an area where risk prediction is particularly important, and remains an ongoing area of clinical relevance. An online calculator of stroke risk based on data from the European Carotid Surgery Trial is available, and is a further adjunct to clinical decision making (http://www.stroke.ox.ac.uk/model/form1.html).

While not intended to replace clinical judgement in the assessment of individual patients, clinically useful risk stratification by prediction tools provide the clinician with an easy to use method of estimating stroke risk

Transcranial Doppler (TCD) may provide prognostic information based on detection of intracranial stenosis, occlusion or micro-embolic signals (MES).[28,29] In 1,881 TIA patients followed for one year, increased risk of intracranial revascularisation, stroke, myocardial infarction, or vascular death was associated with intracranial stenosis or occlusion detected on TCD, compared to none (adjusted hazard ratio 2.29).[29] Use of 18F fluorodeoxyglucose positron-emission tomography (FDG PET) in large artery stroke may identify high-risk TIA patients based on carotid plaque metabolic activity.[30] A study of TIA and minor stroke patients with symptomatic carotid stenosis showed FDG PET uptake predicted early stroke recurrence, independently of stenosis severity.

Long term prediction of stroke risk after TIA is an area that less data is available for, however a Japanese group has recently shown some predictive ability of the ABCD3-I score (c-statistic 0.61) at three years.[24] However to predict long-term recurrence after TIA, further research is needed. Further external validation of the ABCD3-I score and determination of the role of prediction tools including the ABCD2 score in decision making regarding model of care eg outpatient versus hospitalisation, and cost effectiveness is an area where further research is needed.[31]

Pitfalls in risk prediction

Any risk prediction tool is not intended as a substitute for a careful clinical assessment, and may not be applicable for some sub-groups (eg. young patients with non-atherosclerotic TIA, or posterior circulation TIA). A prospective study of 216 consecutive patients with posterior circulation ischaemic stroke or TIA presenting as emergencies, found that using a conventional ABCD2 threshold of ≥4, approximately 30% of patients who had recurrent posterior circulation events within the first 90 days following stroke or TIA were not identified as being high risk.[32]

To improve risk prediction in posterior circulation TIA further research may focus on external validation of the ABCD2 score in posterior circulation events, or the post-investigation phase ABCD3-I score. Substituting vertebrobasilar stenosis in posterior circulation cases, for the two point scored for carotid stenosis in the ABCD3-I score or incorporating the clinical features vertigo, visual symptoms or ataxia into a risk prediction score may offer potential to refine prediction of stroke following posterior circulation TIA.[31,33]

A limitation of prognostic tools in general is that the majority of outcome events occur in the low or medium risk groups, since the absolute number of events is greater in the low or medium risk group than in the high risk group – 'the prevention paradox'.[34]

Most patients with transient brief neurological symptoms are initially assessed by physicians other than stroke specialists. Typically 50% of patients referred by non-specialists to specialist TIA clinics with transient symptoms have confirmed TIA.[35,36] Establishing a clear diagnosis of TIA may be difficult and a study that examined inter-rater diagnostic agreement between three fellowship-trained vascular neurologists for 55 TIA patients showed only moderate inter-rater agreement was observed, with an agreement coefficient of 0.46 (0.30 to 0.63) when a two point scale ('likely'/'unlikely' TIA) was used.[37] This study highlights the subjectivity of TIA diagnosis, even among stroke specialists, and indicates the need for more objective diagnostic measures.[37] Using TIA prediction tools in patients that have not actually had a TIA may not be helpful to an individual patient. Transient focal neurological episodes in cerebral amyloid angiopathy, sometimes termed 'amyloid spells' can mimic transient ischaemic attacks, but are probably more often related to bleeding (especially superficial cortical siderosis or focal convexity sub-arachnoid haemorrhage) rather than ischaemia.[38] Importantly, such episodes may also herald a high future risk of symptomatic intracerebral lobar haemorrhage, and thus prediction tools for ischaemic stroke would not be anticipated to be useful in this specific scenario.

MRI with diffusion weighted imaging DWI, has been recommended as the preferred imaging modality in TIA, as it has greatest sensitivity for minor ischaemic injury, which informs both diagnosis and risk prediction.[19,31] However availability of scan time and clinical contraindications to MRI may limit its use.

Potential pitfall in the use of prediction tools includes delay in presenting with a TIA and inter-rater variability in assigning the score components of the predication tool – e.g. using incorrect value for blood pressure.[39]

Summary

While not intended to replace clinical judgement in the assessment of individual patients, clinically useful risk stratification by prediction tools provide the clinician with an easy to use method of estimating stroke risk.

The ABCD2 clinical prediction tool is a well validated triage tool in TIA management. Risk prediction in the post investigation phase of TIA management benefits from the incorporation of information gained from imaging e.g. presence of imaging abnormalities on parenchymal imaging or detection of large vessel stenosis. The ABCD3-I score which incorporates imaging information has been shown to improve prediction when compared to the ABCD2 score.

Future work may also need to examine the cost effectiveness and safety of using the ABCD2 score predictive tool in clinical decision making in patients with transient neurological symptoms, as well as determine the external validity of the use of the score by non-specialists or non-physicians and via tele-medicine.

Robust external validation of ABCD3-I score, investigation of the safety and use of acute TIA management algorithms based on ABCD3-I, and research on clinical scenarios in which the utility of prediction tools are unclear (e.g. posterior circulation TIA or TIA in young adults) may be useful next steps for refining risk prediction in TIA.

REFERENCES

1. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, et al. *A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack.* Lancet. 2005;366:29–36.
2. Yang J, Fu JH, Chen XY, Chen YK, Leung TW, Mok V, et al. *Validation of the ABCD2 score to identify the patients with high risk of late stroke after a transient ischemic attack or minor ischemic stroke.* Stroke. 2010 41(6):1298-300.
3. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. *Risk of Myocardial Infarction and vascular death after transient ischemic attack and ischemic stroke.* A systematic review and meta-analysis. Stroke 2005;36:2748-55.
4. Takahashi PY, Dyrbye LN, Thomas KG, Cedeno OQ, North F, Stroebel RJ, et al. *The association of transient ischemic attack symptoms with memory impairment among elderly participants of the third US National Health and Nutrition Examination Survey.* J Geriatr Psychiatry Neurol 2009;22:46-51.
5. Cook CE. *Potential pitfalls of clinical prediction rules.* J Man Manip Ther. 2008;16(2):69-71.
6. Altman DG, Vergouwe Y, Royston P, Moons KGM. *Prognosis and prognostic research: validating a prognostic model.* BMJ 2009;338:b605
7. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. *Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond.* Stat Med 2008;27:157-72.
8. Johnston SC, Gress DR, Browner WS, Sidney S. *Short-term prognosis after emergency department diagnosis of TIA.* JAMA 2000;284:2901-2906.
9. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. *Validation and refinement of scores to predict very early stroke after transient ischaemic attack.* Lancet 2007;369:283-292.
10. National Stroke Foundation. *Clinical Guidelines for Acute Stroke Management 2010.* Melbourne Australia [Cited 2014 August 21]. Available from http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp126.pdf
11. Intercollegiate Stroke Working Party. *National clinical guideline for stroke.* 4th ed. Royal College of Physicians, 2012. https://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf [Cited 2014 August 21]
12. Giles MF, Rothwell PM. *Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores.* Stroke 2010;41:667-73.
13. Sheehan O, Kyne L, Kelly LA, Hannon N, Marnane M, Merwick A, et al. *A population-based study of ABCD2 score, carotid stenosis, and atrial fibrillation for early stroke prediction after TIA.* The North Dublin TIA Study. Stroke 2010; 41:844-5.
14. Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. *Incidence and prognosis of > or = 50% symptomatic vertebral or basilar artery stenosis: prospective population-based study.* Brain. 2009;132:982-8.
15. Coutts SB, Eliasziw M, Hill MD, Scott JN, Subramaniam S, Buchan AM et al. *An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke.* Int J Stroke 2008;3:3-10.
16. Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL, et al. *Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model.* Stroke 2009; 40:181-6.

17. Asimos AW, Rosamond WD, Johnson AM, Price MF, Rose KM, Murphy CV, et al. *Early Diffusion Weighted MRI as a negative predictor for disabling stroke after ABCD2 score risk categorization in transient ischemic attack patients.* Stroke 2009;40:3252-7.
18. Giles MF, Albers GW, Amarenco P, Arsava MM, Asimos A, Ay H, et al. *Addition of brain infarction to the ABCD2 score (ABCD2-I): a collaborative analysis of unpublished data on 4574 patients.* Stroke. 2010;41:1907-13.
19. Merwick A, Albers GW, Amarenco P, et al. *Addition of brain and carotid imaging to the ABCD2 score to improve identification of patients at high early stroke risk after transient ischaemic attack.* Lancet Neurol. 2010; 9(11):1060-9.
20. Chatzikonstantinou A, Wolf ME, Schaefer A, Hennerici MG. *Risk Prediction of Subsequent Early Stroke in Patients with Transient Ischemic Attacks.* Cerebrovasc Dis. 2013;36(2):106-9.
21. Song XK, Wang WJ, Li HY, Ren MS, Wu L, Ma JF. *The value of ABCD3-I score in prediction of cerebral infarction after transient ischaemic attack.* Zhonghua Nei Ke Za Zhi. 2012 Jun;51(6):445-8.
22. Song B, Fang H, Zhao L, Gao Y, Tan S, Lu J, Sun S, Chandra A, Wang R, Xu Y. *Validation of the ABCD3-I score to predict stroke risk after transient ischemic attack.* Stroke. 2013;44:1244-8.
23. Purroy F, Jiménez-Caballero PE, Mauri-Capdevila G, Torres MJ, Gorospe A, Ramírez Moreno JM, de la Ossa NP, Cánovas D, Arenillas J, Alvarez-Sabín J, Martínez Sánchez P, Fuentes B, Delgado-Mederos R, Martí-Fàbregas J, Rodríguez Campello A, Masjuán J. *PROMAPA study: Stroke Project, Cerebrovascular Diseases Study Group, Spanish Neurological Society.Predictive value of brain and vascular imaging including intracranial vessels in transient ischaemic attack patients: external validation of the ABCD3-I score.* Eur J Neurol. 2013;20(7):1088-93.
24. Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S, Ago T, Okada Y, Kitazono T. *Fukuoka Stroke Registry Investigators. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack.* Stroke. 2014 ;45(2):418-25.
25. Cucchiara B, Messe S, Sansing L, et al. *Lipoprotein-associated phospholipase A2 and C-reactive protein for risk stratification of patients with TIA.* Stroke2009;40:2332-2336
26. Macintosh BJ, Lindsay AC, Kylintireas I, Kuker W, Güther M, Robson MD, et al. *Multiple inflow pulsed arterial spin-labeling reveals delays in the arterial arrival time in minor stroke and transient ischemic attack.* AJNR Am J Neuroradiol 2010;31:1892-4.
27. Asdaghi, Negar, et al. *Perfusion MR Predicts Outcome in High-Risk Transient Ischemic Attack/Minor Stroke A Derivation–Validation Study.* Stroke 2013;44.9:2486-92.
28. Moustafa RR, Izquierdo-Garcia D, Fryer TD, et al. *Carotid Plaque Inflammation Is Associated with Cerebral Microembolism in Patients with Recent TIA or Stroke: A Pilot Study.* Circ Cardiovasc Imaging. 2010; (5):536-41.
29. Meseguer E, Lavallée PC, Mazighi M, et al. *Yield of systematic transcranial Doppler in patients with transient ischemic attack.* Ann Neurol 2010;68:9-17.
30. Marnane M, Merwick A, Sheehan OC, Hannon N, Foran P, Grant T, et al. *Carotid plaque inflammation on (18) F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence.* Ann Neurol 2012;71:709-18.
31. Merwick A, Werring DJ. *Posterior circulation ischaemic stroke.* BMJ 2014;348:g3175.
32. Gulli G, Markus HS. *The use of FAST and ABCD2 scores in posterior circulation, compared with anterior circulation, stroke and transient ischemic attack.* J Neurol Neurosurg Psychiatry. 2012;83:2 228-229.
33. Gulli G, Marquardt L, Rothwell PM, Markus HS. *Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: Pooled data analysis from prospective studies.* Stroke. 2013;44:598-604.
34. Stewart LA, Clarke MJ. *Practical methodology of meta-analyses (overviews) using updated individual patient data.* Cochrane Working Group. Stat Med 1995;14:2057–79.
35. Quinn TJ, Cameron A, Dawson J, Lees KR, Walters MR. *ABCD2 scores and prediction of noncerebrovascular diagnoses in an outpatient population. A case-control study.* Stroke 2009;40:749-53.
36. Sheehan OC, Merwick A, Kelly LA, Hannon N, Marnane M, Kyne L. et al. *Diagnostic usefulness of ABCD2 score to distinguish TIA and minor ischemic stroke from non-cerebrovascular events: the North Dublin TIA Study.* Stroke. 2009;40:3449-54.
37. Castle J, Mlynash M, Lee K, et al. *Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists.* Stroke. 2010;41:1367-70.
38. Charidimou A, Gang Q, Werring DJ. *Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum.* J Neurol Neurosurg Psychiatry 2012;83:124-13.
39. Bradley D, Cronin S, Kinsella JA, Tobin WO, Mahon C, O'Brien M, Lonergan R, Cooney MT, Kennelly S, Collins DR, O'Neill D, Coughlan T, Smyth S, McCabe DJ. *Frequent inaccuracies in ABCD2 scoring in non-stroke specialists' referrals to a daily Rapid Access Stroke Prevention service.* J Neurol Sci. 2013;332(1-2):30-4.

MS Society comments on NICE clinical guidelines for MS

Recent National Institute of Health and Care Excellence Guidelines for multiple sclerosis (MS) will block access to important treatments for the condition, the MS Society has warned.

The MS Society welcomed the publication of the guidelines but continues to express concern over access to medication for people with MS. The guidelines reject Sativex and Fampyra because they have not been considered cost-effective. Sativex is a cannabis based medicine proven to relieve painful muscles spasms and stiffness, while Fampyra has been shown to improve mobility. This is particularly disappointing for people with progressive MS as these drugs represent two of only three MS specific treatments available to them.

The MS Society believes the decision to reject Sativex and Fampyra was based on a flawed assessment completed within an inappropriate process. The MS Society has urged NICE to take into account the wider cost benefit of the treatments, such as potential savings in social care costs and called on them to conduct a full technology appraisal of these medicines. The guidelines also fail to include vital references on the use of disease modifying treatments (DMTs) for MS – a significant omission, particularly given the changing landscape in this area with three new treatments licensed last year alone.

However, the MS Society has welcomed significant elements of the guidelines and recognises that NICE have listened to the MS community. For example, the guidelines now recommend that people with MS have an annual review of their treatment and care and stress that people with MS should have access to coordinated care within a team of health and care professionals. These recommendations could significantly improve the treatment, care and support that people with MS receive.

The MS Society believes that this is a significant but important step and the NHS and local authorities should commit the necessary resources to make co-ordinated, reliable care a reality. At a time of already stretched NHS budgets, delivering the guideline recommendations on patient care will be challenging without a commitment to additional investment and resource.

MS Society Chief Executive Michelle Mitchell said, "There is encouraging and disappointing news in these guidelines. Making sure that people with MS are able to access a team of health and care professionals, with a minimum annual review of their treatment and support are important steps and should not be underestimated. It is vital that these recommendations are implemented without delay.

"However, NICE's decision to reject Sativex and Fampyra as treatment options is really disappointing. Surely we should be striving for the most innovative treatment and care to be made available to people with MS, not limiting options even further? The guidelines also fail to stress the importance of the many treatments now available for relapsing forms of MS. This will increase the risk of people with MS not receiving the right treatment at the right time."

MS Society's 'Treat Me Right' campaign found that access to treatments licensed specifically to help people manage the symptoms of MS is abysmally low: just one in 50 people with MS take these. Through the campaign, people with MS are fighting for the right treatment, at the right time, wherever they live.

New evidence on demand for Sativex

A survey of nearly 4,000 people with MS showed the huge gap between people with MS' experience of muscle stiffness and spasms with their access to Sativex. 82% of those who currently take it consider Sativex to be essential or a high priority, but 54% of those who have experienced muscle stiffness and spasms and have never taken it.

Assessing quality of life in Parkinson's in routine clinical settings

Romi Anirban Saha
BMBCh, PhD, FRCP is a Consultant Neurologist at Hurstwood Park Neurological Centre, Brighton and Sussex Universities Hospitals NHS Trust. He is a General Neurologist with a subspeciality interest in movement disorders and has a basic science PhD investigating alpha-synuclein mechanisms of neuronal cell death. He is currently a Service Development Lead in collaboration with movement disorders group at Kings College Hospital and has a formal teaching role at Brighton and Sussex Medical School.

Paul Worth
BM, BCh, PhD, FRCP is Consultant Neurologist at Addenbrooke's hospital, Cambridge. He has a clinical and research interest in Parkinson's disease and movement disorders.

Jon Stamford
BSc, PhD, DSc is Director and Co-Founder of Parkinson's Movement; is a Neuroscientist by training with a double interest in Parkinson's – as a successful researcher in the field and subsequently as a person with Parkinson's. He is Scientific & Advocate Communication Coordinator for the Cure Parkinson's Trust.

Correspondence to:
Dr Romi Saha,
Consultant Neurologist, c/o neurology secretaries,
St Mary's Building (room LG4),
Royal Sussex County Hospital, Eastern Road,
Brighton BN2 5BE, UK.
Email: romi.saha@bsuh.nhs.uk

Conflict of interest statement and Acknowledgements:
Lundbeck Ltd and Teva UK Limited initiated the meetings to discuss quality of life issues in Parkinson's and also funded development of the Consultation Aid. The authors have received honoraria for meeting attendance, but have received no monies for the preparation of this article. Medical writing assistance was provided by Clark Health Communications (funded by Lundbeck Ltd and Teva UK Limited).

Provenance and peer review:
Submitted and externally reviewed.

To cite:
Saha RA, Worth P and Stamford J.
ACNR 2015;14(6);12-14.

For people with Parkinson's, quality of life (QoL) is affected by many factors that are dependent on motor and non-motor symptoms, social support, activity, and environment – making it a difficult subject for clinicians to discuss fully with their patients in a standard outpatient clinic visit. Various definitions for QoL exist, but most recent definitions broadly define QoL as the patient's perception of their life in the context of their environment.[1,2] Physical health remains important, but as part of a broader picture.

Following the principles of patient-centred care, clinicians should also allow their patients the opportunity to discuss their health beliefs, concerns and preferences to inform their individualised care.[3] However, pressures such as limitations on the time allowed for each visit (often only 15–30 minutes),[4] and the intervals between follow-up appointments (average 6–12 months) mean that it is very challenging for clinicians to capture a broad sense of how patients are doing and also focus on specific changes in disease related issues in an efficient fashion without missing something which may be important to patient care and QoL. While this is the case for other chronic diseases, matters can be even more challenging in Parkinson's as the clinical examination findings are dependent on medication timing and the clinic environment, and therefore may not reflect out of clinic function. In addition, there is often a difference between the carer's and the patient's perspective, which may be confounded by mood and cognitive function.

Continuity of care is also important and it is vital that clinicians document how the patient's health status changes over time; one way to do this would be to assess and record patient-reported changes in their symptoms and how these impact their daily life at each appointment. Many QoL scales and tools, including the PDQ-39[5] and its shorter version the PDQ-8[6] have been developed, but are not routinely used in most clinical practices, mainly due to length and often perceived lack of user-friendliness. These scales were designed for use in clinical trials where the aim is to collect information systematically and reproducibly. Moreover, in clinical practice, the broad range of detailed questions may distract from a much smaller number of issues of greater relative importance to the patient.

Using their consultation skills, most clinicians will start the conversation with an open question, although it can often take repeated prompting to get to the troublesome issues and some may still be missed.[7] It can be especially difficult to identify the most important issues as patients are not always aware of all the potential motor and non-motor symptoms attributable to Parkinson's. Recent studies show that non-motor symptoms remain under-recognised,[8] and that patient understanding of motor symptoms such as the meaning of 'wearing-off' is still lacking.[9]

A recent survey by The Cure Parkinson's Trust (CPT) asked people with Parkinson's to say whether they felt that their Parkinson's specialist listened to their priorities. A total of 77 patients responded, of whom 69% reported that their specialist 'always' or 'mostly' listened to their priorities. However, 31% said they felt that their priorities were only 'sometimes', 'rarely' or 'never' listened to. It is worth noting that patients who respond to such polls are likely to be already engaged and educated about their condition and its management, and are therefore more likely to prepare for their visits to the clinic. A problem is how best to engage with the more reticent patients who do not access the information currently available and also for the more engaged patient to prioritise the information they want to get across to their specialist.

To address these issues and improve the quality of the consultation, clinicians may look to other areas of medicine, where simple questions that quickly identify the issues relevant to QoL discussed in a time-pressured consultation have been developed. For example, the Royal College of Physicians has developed three simple questions that assess the control of asthma. Although arguably a less multi-faceted disorder, these questions address symptoms and the impact they have on the ability to perform usual daily activities, and have been shown to correlate with validated QoL tools.[11] Likewise, GPs are now trained to ask patients with any condition to prioritise symptoms so that they can best manage the consultation time (GP curriculum section 2[12]), but this is not automatically done in neurology and care of the elderly clinics where practitioners are often more focused on specific issues such as driving, presence of impulse control disorders (ICDs), dyskinesia, medication side effects, atypical disease features etc. rather

than having the time to establish what is most important to the patient's function and QoL.

In the case of a Parkinson's consultation, simple opening questions such as 'What has changed since we last discussed your Parkinson's?' and 'Have these changes caused you or your family any particular problems?' might be effective in starting to tease out the problems that are troubling patients as well as establishing any other changes in social circumstances and environment likely to impact on function and QoL. This approach is also more likely to pick up non-motor symptoms, which the patient and/or carer may have not realised were part of Parkinson's. This approach would go hand in hand with patient education regarding the wide range of signs and symptoms that are characteristic of Parkinson's and will in turn maximise the usefulness of future consultations, as both physician and patient/carer will be better prepared to identify and discuss their most troublesome symptoms. In this respect, pioneering studies in the Netherlands show that proper patient (and carer) education can itself significantly improve QoL in Parkinson's.[13]

One simple approach to improving the efficiency of the consultation is to ask patients to prepare for their next appointment by considering what they want to talk about before they come. Patient diaries are available for motivated patients to capture both motor and non-motor symptoms over the course of several days, but this may provide reams of information over months which may not be easy to analyse in the consultation, only looked at in a cursory fashion or put to one side with patients disappointed that their efforts have not been useful. Instead, it may be easier in the first instance for patients simply to list symptoms that bother them. They should also be directed to symptoms that may be related to disease and likely to affect QoL but that they may not have linked to their Parkinson's and so not mentioned. In order to help address patients' most important symptoms and QoL concerns, and to try to bring some structure to the consultation and thereby get the most out of the limited time available, a group of experts set out to design a simple consultation aid that could facilitate a patient's preparation for, and participation in their routine clinic visits. The group included a range of Parkinson's specialists including Neurologists, Geriatricians, Parkinson's Nurse Specialists and representatives of CPT and Parkinson's Movement (including an expert patient; JS).

The Parkinson's QoL Consultation Aid includes 17 prompts or domains/groups of symptoms, relating to Parkinson's itself, and its potential impact on activities of daily living and QoL. These domains were identified through review and discussion of the domains captured in available QoL of life tools (both disease specific and generic), and were also informed by a CPT survey highlighting factors that typically more strongly determine QoL measures. The domains are not exhaustive, and the tool was purposely not designed to be a list of symptoms. Instead, the Consultation Aid guides the patient to think about the areas of life that Parkinson's can affect and encourages them to think beyond pure motor function. The arrangements of the prompts are deliberately disjointed such that patients can think of them independently and not necessarily make links implying association or cause between certain symptoms and functions/activities. The graphic use of the clock provides a way of discussing both change over time, either positively or negatively, reflecting both a progressive neurodegenerative disease but also response to therapies and also to help with prompting the clinician to ask whether the symptoms change over 24 hours leading to identification of wearing off. Where appropriate or relevant, patients are encouraged to consider the prompts with carers which provides a way of discussing factors influencing both the patients and carers perspectives on QoL. After this patients are asked to consider the three most important areas for discussion with their clinician. The Consultation Aid can be sent to patients in advance of the consultation, filled out just prior to the consultation or use during the consultation itself.

The carer perspective is crucial to QoL discussions. Members of the development group have 'road-tested' the Consultation Aid and used it during the outpatient clinic visit itself to act as a series of prompts for facilitating QoL discussions with the carer present. This has improved the quality of the conversation with both patients and carers leading to greater consultation satisfaction without necessarily increasing the time of the consultation. Indeed, the Consultation Aid provides a way of accessing important information in a more time efficient and patient-centred fashion. In the majority of cases, use of the

Making the most of your appointment

To help discussion, you might like to consider how Parkinson's impacts your lives:

- Things that have got better
- Things that have got worse
- Any other concerns?

Note down the top 3 things you'd like to discuss below:

1. _____

2. _____

3. _____

What would you like to talk about?

This concept originated from The Cure Parkinson's Trust (CPT) and an expert group of healthcare professionals at advisory boards.
Lundbeck Ltd/Teva UK Limited initiated the meetings and funded production of materials.
CPT registered charity number: 1111816

January 2014
TLUK/AZT/13/0027b

Consultation Aid provided important information that would not otherwise have been volunteered. These 'hidden' symptoms typically include fatigue, pain, communication, sexual dysfunction and mild cognitive symptoms and also provide broader understanding of the impact of Parkinson's on social function and sense of isolation. Alternatively the Consultation Aid can be used in advance of the outpatient visit, in which case patients have been informed that they may find it helpful to review some of the prompts with their carer/partner as well. The use of the Consultation Aid given immediately in advance of the appointment to be considered in a busy waiting area has proven to be of less utility in this regard. The relatively small number of patients and carers on which this aid has been tested have found the Consultation Aid easy to understand, the rationale easy to comprehend, and have reacted positively with almost universal approval. The use of the Consultation Aid does not seem to have generated undue distress at prompts, which are mentioned on the aid but not yet experienced by the patient.

Of course, doctors will continue to ask about all aspects of Parkinson's as part of good consultation practice. Many tools are available to assess specific aspects of a patient's condition for example NMS-QUEST or NMSS[14] to assess non-motor symptoms and WOQ-19[15] to assess wearing-off. The Consultation Aid is not designed to replace these but rather to engage the patient in a prioritised conversation around QoL. When reviewed with local patient support groups, the Consultation Aid was perceived favourably as helping facilitate a patient and carer centred consultation.

Copies of the Parkinson's QoL Consultation Aid in both colour and black and white are freely available and can be printed via Parkinson's Movement at CPT website (www.cureparkinsons.org.uk/ the Consultation Aid can specifically be found here: www.cureparkinsons.org.uk/Sites/parkinsons-movement/pages/quality-of-life-tool). It is recognised that each clinician will have a different consulting style and technique and the use of such a consultation aid will depend on both patient factors and clinical settings. However, in the experience of those who have used it, it has proved to be a valuable adjunct to consultations with Parkinson's nurses, elderly care specialists and neurologists. Any meaningful improvement in the consultation will underpin better patient care in a resource effective fashion.

The use of the Consultation Aid can be audited by using the standard Royal College of Physicians or General Medical Council outpatient consultation patient satisfaction questionnaires (commonly used by UK physicians as part of their appraisal and revalidation requirements), and although this may help indicate patient satisfaction with the consultation it may not necessarily measure the impact on QoL. To audit this a validated measure such as the PDQ-39[5] questionnaire would need to be used both at baseline and after any changes in management that follow the use of the Consultation Aid. This would then need to be compared to a cohort of patients in whom the Consultation Aid was not used. This would be a major undertaking and the more pragmatic step adopted has been to undertake a standard consultation and then use the Consultation Aid at the end of the consultation discussions to see if any additional information comes to light which may positively influence QoL conversations.

Expert working group who were involved in the design and testing of the Consultation Aid:

- Dr Romi Saha, Consultant Neurologist, Brighton and Sussex University Hospitals NHS Trust
- Dr Paul Worth, Consultant Neurologist, Cambridge University Hospitals NHS Foundation Trust
- Jon Stamford, Parkinson's Movement, The Cure Parkinson's Trust, www.cureparkinsons.org.uk/sites/parkinsons-movement
- Helen Matthews, The Cure Parkinson's Trust, www.cureparkinsons.org.uk/
- Dr Peter Fletcher, Consultant Physician in Elderly Care, Gloucestershire Hospitals NHS Foundation Trust
- Dr Doug MacMahon, Consultant Physician, University Hospitals Coventry and Warwickshire
- Annette Hand, Nurse Consultant, Northumbria Healthcare NHS Foundation Trust
- Anne Martin, PDNS Kings College Hospital Parkinson's Centre of Excellence, London.

REFERENCES

1. World Health Organisation (WHO). *WHOQOL measuring quality of life.* 1997. Available for download at http://www.who.int/mental_health/media/68.pdf
2. University of Toronto. *The Quality of Life Model* http://www.utoronto.ca/qol/qol_model.htm
3. National Institute for Health and Care Excellence (NICE). *Quality standard for patient experience in adult NHS services QS15.* http://guidance.nice.org.uk/QS15. 2012.
4. Royal College of Physicians. *Consultant physicians working with patients,* revised 5th edition. London: RCP, 2013.
5. Peto V, Jenkinson C, Fitzpatrick R. *PDQ-39: A review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures.* J Neurol 1998;245 Suppl 1:S10-4.
6. Jenkinson C, Fitzpatrick R, Peto V, Greenhalf R, Hyman N. *The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire.* Psychol Health 1997;12(6):805-14 .
7. Kurtz SM, Silverman J, Draper J. *Teaching and learning communication skills in medicine.* Radcliffe Medical Press (Oxford). 2005.
8. Hu M, Cooper J, Beamish R, Jones E, Butterworth R, Catterall L, Ben-Shlomo *Y. How well do we recognise non-motor symptoms in a British Parkinson's disease population?* J Neurol 2011; 258(8):1513-17.
9. Matthews H, Stamford J. *OFF-PARK: Impact of wearing-off symptoms on quality of life; matched survey of both people with Parkinson's (PWP) and their care partners.* Poster presented at the 3rd World Parkinson Congress. Montreal, Canada 2013.
10. *The Cure Parkinson's Trust survey.* 2013. Available at: https://healthunlocked.com/parkinsonsmovement/polls/130020884/do-you-feel-your-priorities-were-listened-to-by-your-parkinsons-specialist/result
11. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. *Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 questions'.* Prim Care Respir J 2009;18(2):83-8.
12. Kular M. *Consultation Skills - Control the length of the consultation.* GP Magazine December 2009 http://www.gponline.com/Education/article/972407/consultation-skills-control-length-consultation/
13. A'Campo LE, Spliethoff-Kamminga NG, Roos RA. *An evaluation of the patient education programme for Parkinson's disease in clinical practice.* Int J Clin Prac 2011;65(11):1173-9.
14. NMS-Quest and NMSS available via the international Parkinson's Disease Non-Motor Group. http://www.pdnmg.com/
15. Stacy M and Hauser R. *Development of a patient questionnaire to facilitate recognition of motor and non-motor wearing-off in Parkinson's disease.* J of Neural Transm 2007;114:211-17.

biogen idec

TECFIDERA® (DIMETHYL FUMARATE) A FIRST-LINE ORAL TREATMENT FOR MULTIPLE SCLEROSIS

TECFIDERA® (dimethyl fumarate) is a **new oral treatment** for adult patients with **relapsing-remitting multiple sclerosis** (RRMS),[1] the most common type of MS.[2]

TECFIDERA is **taken twice daily with food**.[1]

TECFIDERA is accepted by the Scottish Medicines Consortium (SMC) for use in Scotland for adult patients with relapsing-remitting multiple sclerosis (RRMS).[3]

The **National Institute for Health and Care Excellence** (NICE) has issued the **Technology Appraisal Guidance** (TAG) for TECFIDERA. The TAG states that NICE recommend TECFIDERA as **an option for treating adults with active RRMS** – normally defined as 2 clinically significant relapses in the previous 2 years – only if, they do not have highly active or rapidly evolving severe RRMS. TECFIDERA will be provided under a **patient access scheme.[4] The NHS now has until 27th November 2014 to implement the guidance.**

TECFIDERA has been clinically shown to help reduce important measures of disease activity:

Significantly reduce the rate of MS relapses by 53% (0.17 vs. 0.36, p<0.001)[5] and 44% (0.22 vs. 0.40, p<0.001)[6] vs. placebo at 2 years.

27%[5] and 29%[6] of patients on TECFIDERA had an MS relapse in 2 years, vs 46%[5] and 41%[6] of patients treated with placebo (p<0.001).[5,6]

Significantly reduce the number of gadolinium-enhancing lesions on MRI by 90% (0.1±0.6 vs. 1.8±4.2, p<0.001)[5] and 74% (0.5±1.7 vs. 2.0±5.6, p<0.001)[6] vs. placebo at 2 years.

After 5 years, 88% of patients continuing treatment were free of gadolinium-enhancing lesions.[7]

Reduce the risk of 12-week sustained disability progression by 38% (16% vs 27%, p=0.005)[5] and 21% (13% vs. 17%, p=not significant)[6] vs. placebo at 2 years.

After 5 years, risk of 24-week sustained disability progression remained low (19%, [95% CI, 15-22%]), as measured by 24-week confirmed EDSS).[8]

Patient-reported health-related quality of life scores were statistically significantly improved vs. placebo at 2 years (mean changes relative to baseline in physical and mental component summary scores were p≤0.0001 and p<0.05, respectively).[9]

It is believed that **TECFIDERA may provide a new approach to treating MS** by activating the Nrf2 pathway, although its exact mechanism of action is not fully understood. This pathway provides a way for cells in the body to **defend themselves against inflammation and oxidative stress** caused by conditions like MS.

TECFIDERA has been **shown to demonstrate an acceptable safety profile in RRMS patients** over 5 years.[10] The most common side effects for TECFIDERA are flushing and gastrointestinal problems (i.e., diarrhoea, nausea, abdominal pain, upper abdominal pain). These side effects tend to begin early in the course of treatment and may continue to occur intermittently throughout treatment.[1] Appropriate supportive therapy may help manage these side effects.[11,12]

References:

1. TECFIDERA (dimethyl fumarate). Summary of Product Characteristics. July 2014
2. Multiple Sclerosis Society. Relapsing Remitting (RRMS). Available at http://mssociety.org.uk/what-is-ms/types-of-ms/relapsing-remitting-rrms [Accessed April 2014]
3. Scottish Medicines Consortium. Dimethyl fumarate (TECFIDERA) for the treatment of adult patients with relapsing remitting multiple sclerosis. 7th April 2014
4. NICE. Multiple sclerosis (relapsing-remitting) – dimethyl fumarate – Technology Appraisal Guidance (TAG). 2014
5. Gold, R. et al. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. NEJM 2012;367:1098-107
6. Fox, J.R. et al. Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis. NEJM 2012;367:1087-97
7. Arnold, D. et al. 5-Year Follow-up of Delayed-Release Dimethyl Fumarate Treatment in Relapsing-Remitting Multiple Sclerosis (RRMS): MRI Outcomes From DEFINE, CONFIRM, and ENDORSE. Poster presented at: 2014 Joint ACTRIMS-ECTRIMS meeting; September 10-13, 2014; Boston, Massachusetts, USA. Poster 059
8. Gold, R. et al. 5-Year Follow-up of Delayed-Release Dimethyl Fumarate in Relapsing-Remitting Multiple RRMS: Integrated Clinical Efficacy Data From DEFINE, CONFIRM, and the ENDORSE studies. Poster presented at: 2014 Joint ACTRIMS-ECTRIMS meeting; September 10-13, 2014; Boston, Massachusetts, USA. Poster 110
9. Sarda, S. et al. Health-Related Quality of Life in Relapsing-Remitting Multiple Sclerosis (RRMS): Comparison with Other Medical Conditions and Effect of Delayed-Release Dimethyl Fumarate Treatment. Poster presented at: 66th Annual Meeting of the American Academy of Neurology; April 26 - May 3, 2014; Philadelphia, Pennsylvania, USA. P4.182
10. Pozzilli, C. et al. Long-term Follow-up of the Safety of Delayed-Release Dimethyl Fumarate in RRMS: Interim Results from the ENDORSE Extension Study. Poster presented at: 2014 Joint ACTRIMS-ECTRIMS meeting; September 10-13, 2014; Boston, Massachusetts, USA. Poster 066
11. Fox, E. et al. Gastrointestinal Tolerability of Delayed-Release Dimethyl Fumarate in a Multicenter, Open-Label Study of Patients With Relapsing Forms of Multiple Sclerosis. Neurology, 2014; 82 (10): Supplement P2.227
12. Phillips, J.T. et al. Managing Flushing and Gastrointestinal Events Associated with Delayed-Release Dimethyl Fuarate: Experiences of an International Panel. Multiple Sclerosis and Related Disorders 2014;3:513-519

Prescribing Information: Tecfidera® (dimethyl fumarate) 120 mg and 240 mg gastro-resistant hard capsules

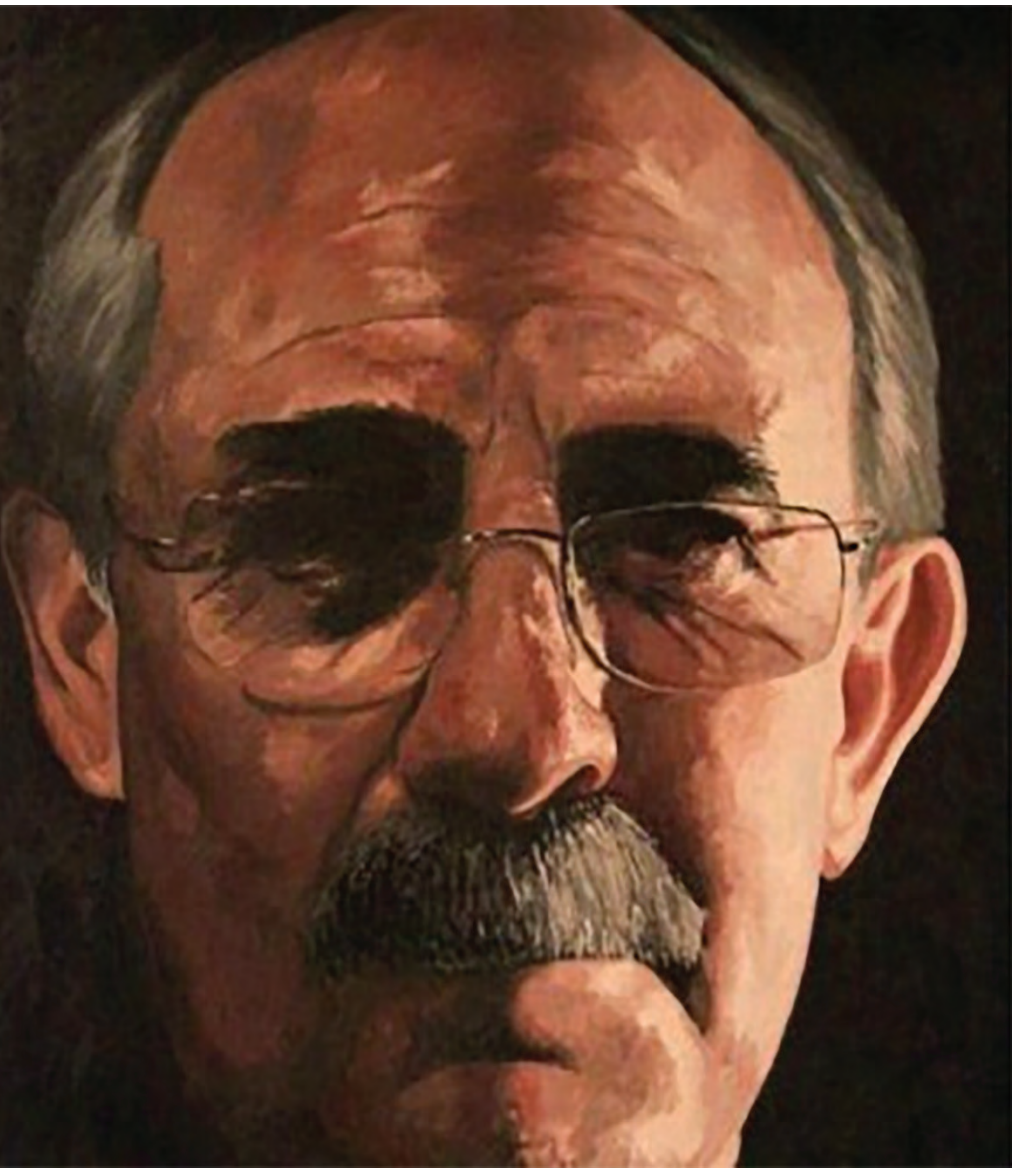
Please refer to the Summary of Product Characteristics (SmPC) for full information. **Indication:** Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS). **Dosage and Administration:** Starting dose of 120 mg twice a day, increased to recommended dose of 240 mg twice a day after 7 days. To be taken orally with food. **Contraindications:** Hypersensitivity to dimethyl fumarate or to any excipients. **Special Warnings and Precautions:** Exercise caution in patients with pre-existing low lymphocyte counts, as Tecfidera may decrease lymphocyte counts. A recent complete blood count (within 6 months) should be available prior to initiating treatment with Tecfidera, and further assessments are recommended after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated. Changes in renal and hepatic laboratory tests have been seen in subjects treated with Tecfidera in clinical trials. Renal and hepatic function assessments are recommended prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated. Use with caution in patients with severe renal or hepatic impairment, or patients with severe active gastrointestinal disease. Prescribers and patients should be alert to the possibility of hypersensitivity or anaphylactoid reactions in the event of severe flushing reactions. Consider treatment suspension in the event of serious infection; reassess benefit/risk prior to resuming therapy. **Drug interactions:** Concomitant use of Tecfidera with a short course of IV corticosteroids was not associated with an increase in infection. IM interferon beta-1a, glatiramer acetate and oral acetylsalicylic acid did not alter the pharmacokinetic profile of dimethyl fumarate. Simultaneous use of other fumaric acid derivatives should be avoided during treatment with Tecfidera. Concurrent therapy with nephrotoxic medicines may increase the potential of renal adverse reactions in patients taking Tecfidera. Consumption of large quantities of strong alcoholic drinks may increase the frequency of gastrointestinal adverse reactions. Interaction studies with vaccines and oral contraceptives have not been performed. **Pregnancy and lactation:** There are no or limited data from the use of dimethyl fumarate in pregnant women. Tecfidera is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk; a risk to newborns/infants cannot be excluded. The benefits of breastfeeding for the child and therapy for the woman should be considered when deciding whether or not to discontinue Tecfidera therapy. **Undesirable Effects:** The most common adverse reactions were flushing (generally mild to moderate severity, <1% of patients had serious flushing) and gastrointestinal events - diarrhoea, nausea, abdominal and upper abdominal pain (serious GI events including gastroenteritis and gastritis seen in 1% of patients). Other events reported commonly included lymphopenia (lymphocyte counts <0.5 x 109/l seen in 6% of patients treated with Tecfidera), leucopenia, vomiting, dyspepsia, pruritus, rash, erythema, proteinuria, ketones/albumin in urine, raised LFTs [transaminases >3xULN in 6% (ALT) and 2% (AST) of patients], reduced WBC count. See SmPC for full list of adverse events. **Legal Classification:** POM. **Pack Size and Price:** 120 mg capsules x 14 £343.00; 240 mg capsules x 56 £1373.00. **Marketing Authorisation Numbers:** EU/1/13/837/001-002 **Marketing Authorisation Holder:** Biogen Idec Ltd, Innovation House, 70 Norden Road, Maidenhead, Berkshire SL6 4AY, United Kingdom. **Date of last revision of Prescribing Information:** August 2014.

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 Biogen Idec on 0800 008 7401.

TF-GBR-0105 October 2014

Dr Chris Allen

Interview by GEMMA CUMMINS | Portrait by Paul Cash



A CAREER HIGHLIGHT Realising, about 15 years after being appointed a Consultant Neurologist at Addenbrooke's and five years after being appointed Clinical Dean in the University of Cambridge, that there was no place I would rather be in my career. I was a clinician working in a world class research centre, surrounded by the stimulation of young research students and clinical students and yet still spending much of my time in direct contact with patients.

BIGGEST REGRET That I probably never will write that novel, otherwise I refer readers to Edith Piaf.

INSPIRING MENTOR Michael Harrison (at the Middlesex hospital), probably the best Neurologist of his generation and certainly the nicest, he inspired me in many ways personally and neurologically.

MOST MEMORABLE PATIENT There have been many, memorable for different reasons. One lasting impression was left by a patient with metastatic cancer I met as a clinical student. He said "I hope you're not going to tell me I only have months to live, because some idiot of a doctor told me that 4 years ago!" This taught me never to specify any person's lifespan…doctors are usually wrong when they try to guess how long someone has to live.

IF I HADN'T BEEN A NEUROLOGIST When I was 10 years old, admiring my father, I wanted to be a fighter pilot. At school I was mainly interested in literature and art but good at biology, so medicine seemed to be a good practical choice. At various stages as an undergraduate I wanted to be a Psychiatrist, a Paediatrician and General Physician (internist) in that order (I never saw myself as a Surgeon). I only decided to commit to being a neurologist after nearly five years working post qualification in various medical specialties including two years as a general medical registrar. Already having an intellectual interest in the brain I realised that in neurology I would be able to practice the clinical method in its ultimately satisfying form, now aided by increasingly sophisticated neuroscience and imaging. Remember I started as a medical undergraduate the year levodopa was introduced as a treatment for Parkinson's disease and qualified in the year CT imaging of the brain was introduced into clinical practice.

I now see that if I hadn't become a neurologist I would have been very disappointed with my life (unless I had written that novel).

HIDDEN TALENT Having so few I prefer not to hide any talent I think I have!

ADVICE TO BUDDING CHARCOTS (IE TRAINEE NEUROLOGISTS) Never let someone else direct your career, believe in yourself but check your ambitions against reality. Try to end up doing something you are good at rather than something you wish you were good at. Disappointment in careers arises from a mismatch in a person's ambition and his/her ability to achieve it. Take advice from multiple sources and then see what these different sources have in common. Always consider whether someone is advising you for their own benefit or yours. There is a lot of luck involved in the evolution of someone's career but luck favours the prepared.

3 MOST IMPORTANT QUALITIES IN A NEUROLOGIST He or she must be an empathetic physician. You must combine your knowledge of the science of disease and your clinical skills at identifying it with compassion for the individual, treating the patient and not the disease. Apply the scientific method to understand the disease and with this use human compassion to manage the patient's illness. Try to be the neurologist you would like to consult.

NEXT FRONTIER IN NEUROSCIENCE IS… If I predict this I will be wrong. However I suspect it will be in the territory furthest from our understanding now, which is the frontier between the brain and the mind (and whether this is a discoverable border after all).

GUILTY PLEASURE Eating too well. I don't feel guilty about drinking too well and I've given up smoking long ago….as to other pleasures I feel no guilt.

FAVOURITE TIPPLE IN FAVOURITE PLACE A glass of American IPA anywhere with one or more of my grown up children, one a Neurologist, one a Clinical Psychologist and one on his way to becoming a Psychiatrist and all three, with their partners, my closest

friends and the parents of my (soon to be) five grandchildren.

FAVOURITE QUOTE Voltaire is reported to have said "The effective physician is one who successfully entertains the patient whilst nature effects a cure". When I told this to a neurosurgical colleague he said "I suppose you will be saying that the effective surgeon is one who successfully entertains himself whilst nature effects the cure".

MOST EMBARRASSING MOMENT When, on my first ward round as a clinical student at Guy's Hospital, I realised that the zip on my trouser fly had totally failed.

MOST CHERISHED POSSESSION (APART FROM FAMILY) My Bamboo handled "Queen Square" style tendon hammer, a chimeric object derived from multiple sources over thirty years. It does more than obtain reflexes, it is my totem. Generations of registrars have been trained to retrieve it from lost regions of the hospital.

FIRESIDE READ Novels by the new generation of Indian and British Indian authors such as Amulya Malladi, Vikram Chandra and Amitav Ghosh.

PAINTING I WOULD LIKE ON MY WALL A good one that I had painted, another unrealistic ambition, failing that "Sainte-Victoire Dagı" by Cezanne or David Hockney's "Woldgate Woods".

DESERT ISLAND PLAYLIST I would take a collection which reminded me of various stages in my growing up:

1. Harry Belafonte "The banana boat song (Day O)." My father would play this frequently whilst I was a child growing up in India, where he worked as a Tea Planter. My father was the greatest man I have ever known, my icon still.
2. Cliff Richard "Livin' lovin' doll." This came out when I was nearly 11 and my older brother played it endlessly in the school holidays.
3. Charlie Parker "My old flame." Charlie Parker was my musical obsession at 16 when I was wrestling with the choice of whether to do science A levels or English and History.
4. Beatles "Love me do." This peaked in the British charts at the same time as my last holiday visit to my parents in India; it marked the beginning of the crazy 1960's as far as I was concerned.
5. Rolling Stones "Get off of my cloud." A reminder of my somewhat disorganised life as an undergraduate.
6. Credence Clearwater Revival "Down on the Corner" Would remind me of more time in the "wasted" part of my youth.
7. Cat Stevens "Morning has broken." My long suffering wife was a Cat Stevens fan when we met and this was played at our wedding in 1973.
8. Mozart Bassoon Concerto in B flat major, K. 191/186. I played Mozart cassettes nearly continuously in the car when travelling around East Anglia in anticipation of applying for my consultant post involving clinics in Cambridge, Peterborough and Kings Lynn.

DINNER PARTY GUEST LIST

1. Ray Tallis
2. Kate Petheram (my eldest daughter, a Neurologist)
3. Sam Allen (my son, future Psychiatrist and a talented cook)
4. JK Rowling
5. Joanna Allen (my daughter, a Clinical Psychologist)
6. David Hockney
7. Susie Allen (my wife, a Child Psychotherapist)
8. Iain McGilchrist
9. Rebecca Shaeffer (my American daughter-in-law, a Human Rights Lawyer).

Researchers develop 3D printed foot orthotics

Glasgow Caledonian University (GCU) researchers, in partnership with the University of Newcastle and Newcastle-based SME Peacocks Medical Group, have been awarded significant funding for the design and manufacture of innovative foot orthotics using 3D-printing technologies.

The project has been granted a £77,000 Small Business Research Initiative (SBRI) Healthcare development contract. SBRI Healthcare is an NHS England initiative, championed by the newly formed Academic Health Science Networks to develop innovative products and services that address unmet health needs.

The funding was awarded following a call to address challenges in improving diagnosis, self-management and prevention of musculoskeletal disorders.

Disabling foot and ankle conditions affect approximately 200 million European citizens. Over €300 million per annum is spent treating many of these people with orthoses and splints, often relying on hand-crafted manufacturing techniques which are slow, costly and difficult to reproduce.

With an increasingly ageing population and a growing health burden in long-term conditions, the global market for custom foot orthoses continues to grow.

The GCU team, led by Dr Gordon Hendry and Professor Jim Woodburn, will work with Peacocks Medical Group and researchers from Newcastle University on the 'FootFEMan' project, which will utilise a computational engineering tool called finite element analysis to improve the functional design of orthotic devices for individual patients.

The improved personalised design will then be printed layer by layer using 3D-printing techniques developed previously in the team's award-winning EU-funded project, A-FOOTPRINT.

Dr Hendry said "We are confident that we can successfully 3D print new orthotic insole devices. This project will now enable us to improve each orthotic tailored to the individual patient according to whatever foot problem they have.

"We will test the new products in controlled clinical studies here at GCU to see if we can improve foot function during walking and further lessen disabling foot symptoms."

Professor Woodburn added: "GCU's collaborative partnership with Peacocks will enable them to maintain and grow their market position as the leading SME developing innovative and knowledge-based orthotic products."

For more information, E. Fiona.ramsay@gcu.ac.uk

It ain't what you do, it's the pace that you do it...

Reviewer – Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust, UK

There is an unwritten law of rehabilitation research that the more obviously beneficial an intervention, the harder it can be to identify a good evidence base. Is it better for Speech Therapists to conduct therapy sessions using the same language as the patient they are working with? Are the outcomes for hydrotherapy better in warm rather than freezing water? No, I don't know either. There's no evidence to say so, we just assume.

There is certainly a lot of research around the levels of physical activity within inpatient rehabilitation units. Perhaps unsurprisingly many patients are observed to spend significant amounts of time being physically inactive in spite of the fairly well evidenced(!) benefits of physical activity in a number of different domains. Engaging in social interaction is also felt to be important in the context of rehabilitation, but with a significantly less-well developed evidence base. The researchers begin this interesting study of the effects of environment on stroke recovery with reference to animal models. Although there is probably something to be said for drawing analogies around neuronal remodelling and cellular changes from mouse models of stroke, determining what constitutes an ideal environment for social activity from murine preferences is probably a less secure paradigm. The idea of an "enriched environment" is a fairly nebulous one but most of us would intuitively feel there is value in a setting that promotes social interaction and cognitive activity.

In order to determine the benefit of an "enriched environment" two (fairly small) groups of stroke patients within an inpatient neurorehabilitation facility were compared. One group were given access to communal activities and individual opportunities for stimulation such as newspapers, games consoles, board games, music and books. The other group received "standard care" (one wonders how rigorously the control group could be denied personal stimulation). Predictably the experimental group spent significantly more time engaged in "activity" than the control group. Unfortunately there is no longitudinal data around the effect that engaging in this activity may have had on length of stay or more meaningful functional outcomes.

No one working within an inpatient care setting can fail to appreciate how the traditional ward environment of being in a bed ministered to passively promotes dependence and adversely affects engaging in the normal activities of daily living. While perhaps animal models are not the best sources of information for the benefits of environmental stimulation in human populations, there are clearly many unanswered questions around the optimum environment for rehabilitation to take place in. Promoting independent social activity and interaction, may, in the end be as important as the regimental daily 45 minutes of face-to-face contact with a therapist in facilitating longer term gains. It is heartening that the focus could switch back to the patient "doing" rather than being "done to" in promoting recovery.

Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, Spratt NJ. An Enriched Environment Increase Activity in Stroke Patients Undergoing Rehabilitation in a Mixed Rehabilitation Unit: A Pilot Non-Randomised Controlled Trial. DISABILITY AND REHABILITATION 2014;36(3):255-62.

Parkinson's Disease

Reviewer – Dr Thomas Foltynie, Consultant Neurologist and Senior Lecturer at the National Hospital for Neurology & Neurosurgery

The quest towards finding a neuroprotective agent for Parkinson's disease continues apace. The two main strategies can be broadly separated into those which aim to identify "de-novo" drugs with a specific action on the neurodegenerative process of PD, and those that aim to "repurpose" agents already licensed for the treatment of another human disease, that may have additional relevant effects. The latter strategy has appeal in that agents are far less likely to fail because of intolerable side effects and their efficacy verses futility (on relevant processes such as mitochondrial function or neuro-inflammation) can be determined more quickly and cheaply. There are trials in set-up or in progress using Isradipine, Inosine, Exenatide, Deferiprone, Ursodeoxycholic acid among others as examples of "repurposing".

The former strategy in comparison, is notoriously long-winded in terms of the laboratory selection process, carries high risk of failure because of potential toxicity, and is hugely expensive. It has been estimated that bringing a brand new agent to licensing takes approximately 17 years and costs over $1bn. In the past year however some further progress towards the development of a couple of "de-novo/tailor made" neuroprotective drugs for PD has been made focusing on agents that may have particularly relevance to individual patients with subtypes of PD.

The first targets the LRRK2 protein; mutations in the gene encoding for LRRK2 are the commonest cause of autosomal dominant PD, generally thought to result via a toxic gain of LRRK2 function. The relationship between LRRK2 and PD neurodegeneration appears to be more complex than simply excessive LRRK2 enzyme activity however (LRRK2 includes a GTPase domain, a carboxy terminal domain and a kinase domain and mutations in any of these, including mutations causing a loss of LRRK2 function can all lead to dominantly inherited PD). An important paper published this year by the Sheffield, UK group has suggested that one of the consequences of LRRK2 mutations in either of the first two domains, is on axonal transport via microtubule deacetylation. More importantly they showed that in Drosophila with such LRRK2 mutations (in the GTPase or carboxy terminal domains), enhancing microtubule acetylation through oral administration of a broad acting deacetylating inhibitor -Trichostatin A, could restore axonal transport and could restore abnormal locomotor behaviour even after the motor phenotype was established. Good news for the flies say the cynics…but perhaps also a critical finding towards developing a tailor made agent for patients with specific LRRK2 mutations, and to be considered alongside the concurrent exploration of a range of LRRK2 inhibitors that may have specific utility among the other subgroup of LRRK2 patients with mutations in the kinase domain.

The second paper has relevance for patients with mutations in the GBA gene – the causative gene for Gaucher disease, and recently discovered to also be the greatest single genetic risk factor for PD even when single mutated copies of the gene are inherited. GBA encodes the glucocerebrosidase (GCase) enzyme, and mutations in the gene lead to decreased GCase activity and consequently increased alpha synuclein aggregation. There is great interest in trying to boost GCase function using either repurposed or tailor made agents. AT2101 is an orally available, pharmacological chaperone, a small molecule which can specifically and reversibly bind GCase in the endoplasmic reticulum with high affinity, thus stabilising it, and increasing its trafficking to lysosomes where it has its functional interaction with alpha synuclein. In this paper by the Chesselet group, this AT2101 chaperone had clear effects on GCase stabilisation in an alpha synuclein overexpressing mouse model, which resulted in improved motor deficits and reduction in alpha synuclein neuropathology. This agent has already been the subject of trials in Gaucher patients (unpublished), and may become an agent with major potential relevance to PD neuroprotection in both GBA and possible even in some sporadic PD patients.

Godena et al. Increasing microtubule acetylation rescues axonal transport and locomotor deficits caused by LRRK2 Roc-COR domain mutations. NATURE COMMUNICATIONS 2014. Oct 15;5:5245.

Richter et al. A GCase Chaperone Improves Motor Function in a Mouse Model of Synucleinopathy. NEUROTHERAPEUTICS. 2014. Oct;11(4):840-56.

ALS-FTD. A novel approach

Reviewer – Professor Kevin Talbot, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

In the world of motor neurone disease the C9orf72 hexanucleotide (GGGGCC) expansion mutation remains the centre of attention. It is the commonest single genetic cause of neurodegeneration and serves as a common therapeutic target for up to 10% of all patients with amyotrophic lateral sclerosis and frontotemporal dementia. The potential to alter or block the expression of the aberrant RNA using oligonucleotides makes this the most therapeutically tractable target for ALS therapy. However, despite the intense pace of research in this area, the exact mechanism of toxicity is still unclear. Do RNA aggregates derived from the repeat expansion alter cellular homeostasis by binding to crucial ribonucleoproteins or is neurodegeneration driven by the novel mechanism of dipeptide protein toxicity from repeat associated non-ATG (RAN) translation highlighted in this section last year?[1] A wonderfully elegant approach to answering this question has been recently published by Adrian Isaacs and colleagues at UCL, using the fruitfly eye as a model for toxicity. Taking advantage of the redundancy of the genetic code, they engineered flies in which the five different dipeptides that are predicted to be produced from different reading frames of the sense and antisense strands of the repeat RNA were produced in the absence of repeat RNA. The idea was to isolate protein from RNA toxicity. Similarly they produced repeat RNAs with stop-codons, every 12 GGGGCC repeats, to prevent expression of the dipeptides. The answer was striking. Two dipeptides (GR and PR), both containing arginine led to dramatic death of neurons in the fly eye, while expression of the interrupted, translation deficient, RNA alone did not cause cell death. A potential caveat is that RNA binding proteins are themselves arginine-rich and therefore toxicity from overexpression of arginine dipeptides in this system might be expected to disrupt critical cellular processes. Although this work does not immediately provide a conclusive mechanistic link between arginine dipeptides and ALS, it will serve as an important platform from which to explore the role of dipeptide repeat proteins in patients with ALS-FTD.

[1] Update on the pathogenesis of ALS. Talbot K. ACNR. Volume 13, issue 6, p10.

Mizielinska S et al. C9orf72 repeat expansions cause neurodegeneration in Drosophila through arginine-rich proteins. SCIENCE. 2014 Sep 5;345(6201):1192-4.

ABN Acute Neurology Services Survey 2014

Kevin Talbot
Honorary Secretary, Association of British Neurologists

Kevin Talbot is Honorary Secretary of the Association of British Neurologists, Consultant Neurologist at the John Radcliffe Hospital in Oxford, Professor of Motor Neuron Biology in the Nuffield Department of Clinical Neurosciences, Oxford University and the Director of the Oxford MND Centre. Professor Talbot's research interest is in understanding the molecular basis of motor neuron and other neurodegenerative disorders.

If you, or a member of your family, had an acute and potentially serious neurological problem would you expect to have the benefit of a specialist neurological opinion on the day of your admission to hospital? The Association of British Neurologists (ABN) surveyed all UK Neurologists, who were asked to provide details of their local services, which generated data for 195 acute hospitals across the country. The result is the Acute Neurology Report, the first national survey of acute neurological services, which has just been published by the ABN and reveals that on average across the UK a neurological opinion within 24 hours is only available in just over half of acute hospitals. At worst, in District General Hospitals without a dedicated neurology service, a same-day neurological opinion is only available 30% of the time, on days when a 'visiting Neurologist' is present. The thirty-one Neuroscience Centres in the UK mostly meet the highest quality standards by providing daily neurology specialist review and CT and MRI available 24 hours a day. But there remain a disturbingly large number of hospitals with no neurology service at all, with the Northern region, Northern Ireland, the North West, Wales and the West of Scotland having the most sites with significant gaps in neurology services.

This mixed model of neurology service provision, a reflection of the way the NHS has developed around small local hospitals, District General Hospitals and specialist tertiary referral Neuroscience Centres, inevitably leaves gaps and means the experience of a patient with a neurological illness is determined by geographical location rather than clinical need. It is well established that neurological input leads to improved diagnosis and shorter hospital stays, and it is reasonable to conclude that patients with neurological disorders admitted to hospitals without resident neurologists will have significantly worse access to appropriate investigations and services, which is likely to impinge on the quality of their care.

The ABN has proposed a set of Quality Standards, which define appropriate acute neurology care, and can be summarised as follows:

- There should be access to daily consultation by neurology specialists within 24 hours of admission (if necessary by telemedicine) with care in an appropriate inpatient setting depending on clinical need (including the option of transfer to a neuroscience centre, neurosurgery or intensive care).
- Advice on the management of acute neurological emergencies should be available from a neurology specialist at all times
- Urgent inpatient imaging (CT and MRI), where indicated, should be available
- Lumbar Puncture should be available at all times.
- Rapid access pathways should exist for referral from Emergency Departments and Acute Medical Units to neurology outpatient services

The readers of ACNR will no doubt find these standards simple and obvious and may be baffled that they are not part of every hospital's acute care policy. But the lack of a specific commissioning strategy for neurology has led to inequities in care. Although neurological services have expanded greatly, it is a matter of concern that the provision of inpatient neurological care has been neglected compared to other specialties such as cardiology and gastroenterology, with increased access to outpatient neurological services over recent decades being driven mostly by waiting list targets. Many of the commissioning services and NICE quality standards are disease specific and as a result patients with undiagnosed neurological conditions can be neglected by this process.

A significant step in the right direction would be the adoption by commissioners of the ABN's Quality Standards, so that neurological services can develop to meet the increasing burden of an ageing population.

Atlas of Clinical Sleep Medicine

Pictures for bedtime stories – how a platypus dreams
From within one of the larger sleep services, where we see all sleep disorders – respiratory and neurological, I realise that I may be one of the few UK Neurologists to benefit from the full range of pictures and videos within this book. As a regular teacher on the same range of sleep disorders, one of its best features is excellent online access (to all the pictures, graphs, polysomnography traces and patient videos). There are also several patient interviews – a really useful resource, and a key change to this second edition of the atlas, for a speciality where there are very few physical signs and the history is rarely taught at undergraduate level.

The US based authors have had the luxury of practising Sleep Medicine as a distinct subspeciality for many years. An accredited training programme (and a lucrative polysomnography tariff) has allowed large numbers of full inpatient video polysomnography studies to be performed for all sleep disorders. In the UK and mainland Europe, limited home studies are routinely performed for sleep apnoea screening (constituting the majority of referrals to any sleep service); they are generally less invasive and certainly much cheaper. Information on domiciliary studies of this kind is (inevitably) a weak point in the book.

There are many pages of polysomnography traces which I found helpful, as will my sleep technician colleagues; they will be of little use to those who do not have access to the 'kit'. For epileptologists who also see nocturnal sleep disorders, the standard PSG page (a 30 second epoch, rather than 10 seconds) will take some acclimatisation.

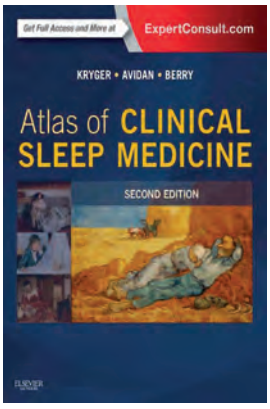
It is unfortunate for the authors that they have published just behind the latest update to the International Classification of Sleep Disorders, which came online in 2014. Immediately, some of the diagnostic categories are outdated, for example in narcolepsy and insomnia.

For Neurologists who routinely miss sleep apnoea in their many patients with chronic disease – simple and quick screening tools like the STOPbang questionnaire will be useful! But they are not particularly easy to find. As usual, the chronic fatigue and fibromyalgia chapter describes sleep disorders as occurring with great frequency in these conditions. Too little is said about the obvious concern that sleep disorders are often the cause of fatigue (which is chronic), and may well be missed, only to be mislabelled unhelpfully as CFS/ME.

The book first covers both normal sleep biology and the standard sleep disorders, and sleep disturbance in common medical conditions, which is a structure it shares with a number of other sleep textbooks. The chapters covering the history and common assessment tools were separated, which did not seem logical.

However, given that this is an atlas, it seems best to judge on the picture and video content, not the text, and these will certainly be useful for clinical workers and teachers in sleep medicine. UK readers will need to allow for the US bias, both in terms of setting up the sleep studies and the available drugs. Overall, like most atlases, this is a book to dip into rather than to read through.

And the platypus? The first video shows a platypus, awake and then dreaming. The platypus has more REM sleep than any other mammal, giving up to 8 hours a day of dreams. Sad to report, this was not nearly as dramatic as I had hoped. Platypus dreams seem far more peaceful than those of our Parkinson's patients!



Authors: Kryger, Avidan and Berry
ISBN: 978-0323187275
Published by: Elsevier
Price: £87.20
Pages: 511

Reviewed by:
Dr Kirstie Anderson,
Consultant Neurologist,
Royal Victoria Infirmary,
Newcastle upon Tyne, UK.

Concussion

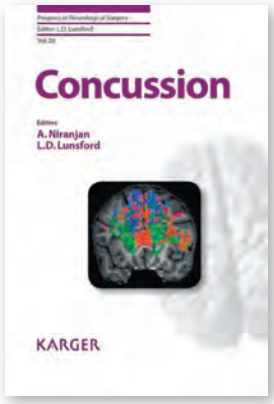
It is not always 'nothing serious'

This book surprised me. Almost immediately, I found myself underlining, and studying, as opposed to simply reading over the text for the purposes of preparing a review. I was struck by how little is still known about concussion and mild traumatic brain injury, and their possible long term sequelae; by the fact that concussion is not always such a minor injury, which may be ignored; and by the importance of a multi-disciplinary approach, and specifically the very central roles of Neuropsychologists, Neurologists and other Physicians, in the management of concussion. Reassuringly, as in most areas of clinical neuroscience, the book underlines how essential diagnosis is for determining treatment. Furthermore, the complexities surrounding the diagnosis of concussion have parallels in other areas of brain injury practice – the uses and limits of new functional brain imaging techniques as compared to the more established role of cognitive testing. On reflection, in a world where sport and conflict (with associated risks of brain injury in general and concussion in particular) are continually covered in the media, it is difficult not to be drawn in by a book that covers these issues

As a general observation about the book, it is very well written, with clear style, relatively easy for non-specialists (in concussion) to follow. This is no doubt in part thanks to chapters being kept short, with a neat abstract, and great illustrations. In places, a personal perspective on concussion (for example chapter 1) also helps to bring to life what might have become overly technical. The broad layout of the book is logical, commencing with conceptual issues and diagnostics, before proceeding to management and rehabilitation. On the downside, some of the chapters, especially the earlier ones on imaging were a bit repetitive, a fault shared by most multi-authored edited texts. At least this provided 'free' revision of the rather complex topics covered in those early sections!

Turning to the specifics, the biomechanical and vector effects involved in concussion were well covered and served as a stark reminder of the dangerous forces at play in head injury, and how clinicians need to understand and consider these when assessing patients. One of the most useful and fascinating concepts outlined, was that of concussion as primarily a physiological (rather than structural) injury of the brain. The implications of this point were explored, including the limits of conventional structural imaging (CT and MRI) in diagnosis. Furthermore, the physiologically injured brain may be especially vulnerable to re-injury, such that repetitive injury to the concussed brain risks chronic traumatic encephalopathy, or even Alzheimer's disease. Accordingly, the chapters on management and rehabilitation, which include robust guidance about 'return to play', were quite gripping and relevant to Neurologists, Neuropsychologists, GPs, Trainers and Physiotherapists.

In summary then, this book grabbed my attention from page 1. My prediction is that most professionals will find plenty to learn within its covers, whether Neuropsychologist, Neurologist or Medic of another hue. It achieves a very good balance between basic science and applied clinical knowledge, in a compact 'package'. The text covers many complexities and technicalities required for grounding in the basic science of diagnosis and rehabilitation of patients with concussion (who are mostly athletes or military personnel), without ever becoming an unwieldy tome. I would recommend it to clinicians and academics alike.



Editors: Niranjan & Lunsford
ISBN: 978-3318026481
Published by: S Karger AG
Price: €165.00
Pages: 256

Reviewed by:
Rudi Coetzer,
Consultant Neuropsychologist,
North Wales Brain Injury Service,
Colwyn Bay Hospital, Betsi
Cadwaladr University Health
Board NHS Wales, UK.

Meningococcal Septicaemia

Diana Mann outside 10 Downing Street

www.meningitis.org

Photo credit: Picture taken by Giulietta Verdon-Roe

I contracted meningococcal septicaemia in 2007 when I was 25, and as a result had both lower legs and all the fingers on my right hand amputated, plus I have epilepsy. I am a member of international charity Meningitis Research Foundation and have been involved in their campaigning to implement a new vaccine against Meningitis B, the strain of the disease I contracted.

Before I became ill I worked with horses, did part-time office work and evening pub work. I was always active, fit and healthy. Meningitis was a disease I had heard of but I had no idea what it could actually do to you and thought it only affected babies and young children. I became ill on a Friday evening whilst working at the pub. I came home, went to bed and don't remember anything else. It was only because my parents came to find me and knew there was something wrong that I am still here today. I was rushed to the Kent and Sussex Hospital in Tunbridge Wells and spent three weeks in intensive care before I was stable enough to be moved to Queen Victoria Hospital in East Grinstead. Over the following weeks I had a number of operations to perform amputations to my legs and multiple skin grafts. I don't remember any of this in detail; I mostly just remember pain. About 50% of me was affected by septicaemia, so the other half needed to be used as donor sites for skin grafts, leaving nearly all of me covered in dressings.

I left East Grinstead three months later and was taken to Queen Mary's Hospital (a specialist rehabilitation unit for amputees) in Roehampton where I stayed for a further three months. I was fitted with limbs, learnt to walk and learnt to cope with the amputations of my right fingers. I had to re-learn simple tasks such as writing, washing, dressing and cooking. There were so many things I used to take for granted that I suddenly found I needed help doing. I left Roehampton in May walking with two sticks and was thrilled! I thought from there on in it would be plain sailing but needless to say I was wrong.

My epilepsy (known as myoclonic jerks) caused small muscle twitches which completely upset my balance and were especially bad on uneven ground, in crowded places, or in the dark. I couldn't ever talk and walk at the same time. Until my Neurologist was able to get these under control, this really hindered my progress. As I started walking more the skin on my stumps began breaking down, so, having only been up and about for a month, I was confined back to a wheelchair and in the September I had a further operation on both stumps to shorten the bone even further. These setbacks were the hardest time for me as I felt like I wasn't making any progress. Some days I didn't want to get up and could very easily have become depressed. I owe a huge thank you to my mum who risked my wrath and came and dragged me out of bed!

It wasn't until Christmas 2008 that I was finally fitted with another pair of legs, over a year after my initial illness. By then I was desperate to start taking control of as much of my life as possible so I moved into a flat of my own. Though not specifically adapted, we had to look hard for somewhere suitable, on the ground floor and with wheelchair access just in case. I had now completed all the obvious short-term goals and the next stage of my recovery was very much down to me.

Fitness was a big problem. I found I got very little exercise and soon became fatter and less fit, which is a common problem for amputees. Walking became more exhausting and the weight gain affected the fit of the prostheses. In 2010 I started riding again having had a hand prosthesis designed and made so I could hold the rein. Horse-riding is a fantastic form of exercise and something I enjoy whilst feeling almost able-bodied. I am now hoping to compete in the Paralympics at Rio in 2016. I have also learnt to ski and to run on prosthetic blades.

Finding a job was difficult as I struggled getting anywhere. Due to my epilepsy, I no longer had a driving licence and I hated having to rely on other people for lifts and found public transport very difficult to use. Then there were access issues and the fact I still needed to attend regular hospital appointments for which I would need time off.

As well as this I was limited to what I could do. The myoclonic jerks from my epilepsy meant I was unable to use a computer as the screen made these significantly worse. Fortunately, as these got better, I was offered a job doing data entry from home, albeit slowly with one hand!

Luckily I have now found more fulfilling roles and in 2012 I worked as a reporter for Channel 4 on the Paralympics and words cannot describe what a fantastic experience this was.

These days the main criteria for work is that it will fit round my riding training. I still do some TV reporting which has also led to motivational speaking and live event announcing. I also work with other amputees doing casualty simulation to help with the training of both the military and emergency services.

Meningitis and septicaemia is not a disease where one day you are ill and the next you are fine. I am back living an exciting and fulfilling life, yet I am also still recovering and will go on doing so for many years to come. The journey I have been through, and the people I have met, has taught me a lot about myself. There is always someone worse off. I have realised what is important to me and appreciate how lucky I am in so many ways. Things are often inconvenient or difficult; I can never do my jewellery up, chopping an onion takes twice as long and I haven't yet found a pair of jeans I like. But I am still just a normal person.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th February, 2015

January

Exercise the 4th cancer treatment: Putting research into practice
13 January, 2015; London, UK
www.royalmarsden.nhs.uk/exercise
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

February

Dementia Update
3 February, 2015; Centre for Life, Newcastle upon Tyne, UK
T. 0191 223 1247
E. northern@rcplondon.ac.uk
http://events.rcplondon.ac.uk/details.aspx?e=3404

Dementias 2015
5-6 February, 2015; London, UK
www.mahealthcareevents.co.uk/dementias2015

The Therapy Outcome Measure (TOM) – 1 day training workshop with Prof Pam Enderby
23 February, London, UK
Royal College of Speech and Language Therapists, London
Delegate fee - £175 (check the event website for discounts for RCSLT members)
For further details and to book go to www.communitytherapy.org.uk

March

Paediatric Palliative Care Study Day
10 March, 2015; London, UK
www.royalmarsden.nhs.uk/paedpalliative
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

National Brain Injury Symposium: Complexity and best practice
13 March, 2015; Royal Hospital for Neuro-disability, London UK
E. institute@rhn.org.uk
www.rhn.org.uk/events/conferences-and-seminars/national-bi-symposium15.htm

An Update on the Effects of Prostate Cancer Treatments on Bladder, Bowel and Erectile Function
13 March, 2015; London, UK (ID 533)
www.royalmarsden.nhs.uk/prostateeffects
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

National Pain Study Day
25 March, 2015 (ID 413); London, UK
www.royalmarsden.nhs.uk/painmanagement
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

NEUROLOGY 2015: leading edge neurology for the practising clinician'
25th March 2015 (half day); 26th March 2015 and Friday 27th March 2015; London, UK
T. 020 344 84460
E. jean.reynolds@ucl.ac.uk
www.ion.ucl.ac.uk

May

Pain Therapeutics
18-19 May 2015; London, UK
www.smi-online.co.uk/pharmaceuticals/uk/pain-therapeutics

ABN 'Need to Know Neurology' Course for GPs 2015
19 May, 2015; Harrogate, UK
E. info@theabn.org

ABN Annual Meeting
19-22 May, 2015; Harrogate, UK
E. info@theabn.org

June

Registrar PD Masterclass
16/17th September, 2015; Sheffield, UK
www.parkinsonsacademy.co.uk
for further details.

Consultant PD Masterclass – Sheffield, UK
Module 1 – 2, 3rd & 4th June 2015
Module 2 – 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk
for further details.

1st Congress of the European Academy of Neurology
20-23 June, 2015; Berlin, Germany
E. headoffice@eaneurology.org

Psychological and Neuropsychological Impact of Paediatric and TYA Cancer on Patients and their Families
29 June, 2015; London, UK
www.royalmarsden.nhs.uk/psychologicalimpact
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

September

Paediatric Oncology Solid Tumours Study Day
14 September, 2015; London, UK
www.royalmarsden.nhs.uk/paedsolidtumours
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

November

Consultant PD Masterclass – Sheffield
Module 1 – 2, 3rd & 4th June 2015
Module 2 – 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk
for further details.

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact info@redpublish.co.uk

The ROYAL MARSDEN
NHS Foundation Trust

Conference and Study Day Programme 2015

Tuesday 13 January 2015
Exercise the 4th cancer treatment: Putting research into practice
http://www.royalmarsden.nhs.uk/exercise
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

Tuesday 10 March 2015
Paediatric Palliative Care Study Day
http://www.royalmarsden.nhs.uk/paedpalliative
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

13 March 2015 (ID 533)
An Update on the Effects of Prostate Cancer Treatments on Bladder, Bowel and Erectile Function
www.royalmarsden.nhs.uk/prostateeffects
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

25 March 2015 (ID 413)
National Pain Study Day
http://www.royalmarsden.nhs.uk/painmanagement
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

Monday 29 June 2015
Psychological and Neuropsychological Impact of Paediatric and TYA Cancer on Patients and their Families
http://www.royalmarsden.nhs.uk/psychologicalimpact
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

Monday 14 September 2015
Paediatric Oncology Solid Tumours Study Day
http://www.royalmarsden.nhs.uk/paedsolidtumours
Venue: The Royal Marsden Conference Centre, Stewart's Grove, London, SW3 6JJ

For further information
Phone: 020 7808 291/2924
Website: www.royalmarsden.nhs.uk/studydays
Email: conferenceteam@rmh.nhs.uk

NHS

The 68th Annual Meeting of the American Epilepsy Society 2014

Conference details: 5-9 December 2014, Seattle, Washington, USA. ***Report by:*** Mark Manford MD FRCP, Consultant Neurologist, Addenbrooke's Hospital.

I set off, leaving my work in the UK, my body arriving in Seattle and my suprachiasmatic nucleus staying stubbornly in mid-Atlantic, waiting to be collected on the way home. In the North West USA I found that we are two nations separated by a common pharmaceutical industry. The drugs clobazam and vigabatrin arriving with much fanfare in the USA at glacial pace after decades in Europe. On the other hand, slow release preparations of oxcarbazepine and topiramate (for epilepsy only, not migraine) being launched in the USA, hopefully the Gulf Stream will get them to us more quickly. The annual course was on the subject of status epilepticus and the key question of the morning was should every single patient in the neuro intensive care have EEG monitoring. Of course they should and there should be an end to all war, poverty and illness too – so I skipped that as being redundant in the real world. I take some consolation that the presentations are from centres of excellence and in Armpitsville Arizona, practice is more what I am used to, with EEG monitoring a wish more than a reality. The science of status epilepticus is becoming evermore interesting – I have reported before that GABA receptors are internalised and stop working after a short time, explaining the failure of benzodiazepines after the initial stages. But NMDA receptors become upregulated and may be responsible both for seizures and neurotoxicity. There was discussion around the use of ketamine in the ITU, as a neuroprotective agent and it was felt that there was some rationale but no evidence. A trial of therapy is just starting in the USA, comparing Phenytoin, Levetiracetam and Valproate. The latest kid on the block with anecdotal successes is IV lacosamide but it will not be included. There was also debate around whether we treat non-convulsive status too aggressively and that in less severe forms of status, the prognosis depends on the cause and the toxicity of drugs is a significant factor.

A year ago, CNN released a documentary called Charlotte's web about Charlotte Figi with Dravet's syndrome (severe myoclonic epilepsy of infancy, often due to a sodium channel mutation) whose treatment failed until she tried "medical marijuana" with miraculous results – see youtube. Since it is only licensed in few states, notably Colorado, this has lead to a migration of hopeful families to said states on the hemp road and not insignificant pressure on the medical profession, which they have responded to in a commendably balanced fashion by doing some science. There were two sessions, including an excellent one featuring researchers from our very own University of Reading, with not a ponytail or a diaphanous scarf in sight. Endocannabinoids are released post-synaptically and feed back on presynaptic neurotransmitter release, producing alterations in temporal and spatial patterns of neuronal excitation. They are implicated in modulating responses to stress and as stress is suggested to be a seizure trigger that may be important. As well as effects on neuronal firing, there are probably trophic effects too, which could be of significance in epileptogenesis. The psychoactive THC moiety can be separated from a potentially anti-epileptic moiety, within the hundreds of cannabinoids that make up Cannabis sativa. There is no doubt that cannabinoids have a useful action on a range of laboratory models of epilepsy. One poster at the conference reported some efficacy in Dravet syndrome but as was wisely quoted to us: "the plural of anecdote is not data". It seems highly likely that trials of the drug will be taken forward and I shall watch this space with interest.

Dravet syndrome also figured in another major theme of this conference, as of all others – genetics. The array of genes is bewildering, to me at least, but we are just starting to see the first tentative steps to personalised medicine. Drugs to avoid in Dravet syndrome are those which block sodium channels, such as lamotrigine and carbamazepine, which are known to make it worse and the logic is clear, given the gene. If this also applies to those cases due to different genes, is not yet clear – whether we shall be treating the phenotype or the genotype is an intriguing question. Prof Anne Berg gave the Lennox and Lombroso lecture pointing out that in these malignant paediatric epilepsy syndromes, data clearly show that very early control of seizures can prevent long term intellectual and social disability, She contrasted the success of the coordination of childhood clinicians in improving cancer outcomes with the lack of anything similar for epilepsy and gave a call to arms to develop systems that allowed these unfortunate children to access tertiary services within days of presentation.

The AES should also be congratulated for setting up a cloud-based resource for researchers to share their information which must be valuable in accelerating the pace of new research and disseminating knowledge, especially in the area of rare genetic conditions.

What have I heard that will change my practice? There is now a large volume of evidence to suggest that the psychosocial morbidity of epilepsy is not just about having a bad time from seizures. It may precede the onset of seizures and long outlast them, even in syndromes where patients may have very few seizures in their lives, such as epilepsy with tonic clonic seizures on waking. Increasingly, I am thinking of epilepsy as a syndrome causing psychosocial dysfunction, in which seizures are just one symptom. I shall be screening my patients for anxiety and depression at each clinic appointment, as it has been demonstrated that my usual: "do they look sad or fidgety?" assessment might not cut the mustard. The Hospital Anxiety and Depression Scale was shown by Hannah Cock and others to be a useful tool and alternatives (which I prefer) are the NIID-E, which they also consider, and GAD-7 assessments. I commend them to you – available on the web. Looking forward to being home again from a slightly lonely and UK depleted AES.

Memorable statistic from the conference: The second commonest cause, after stroke, of days of life lost from neurological disease is from SUDEP. Not as common but strikes young. We need to ensure that our patients are informed sensitively of these risks to help their decision making.

Highlights from the IPSEN Satellite Symposium, 2014 BSRM Annual Scientific Meeting

Innovation in Rehabilitation Medicine

This was the focus of the first ever satellite symposium of the Annual Scientific Meeting of the British Society of Rehabilitation Medicine (BSRM) which explored "Recent advances in neurorehabilitation" and was sponsored by IPSEN. Leading three sessions was Dr Peter Aitken, Chair of the Faculty of Liaison Psychiatry, Royal College of Psychiatry. Dr Aitken began the symposium with a thought provoking talk on "Emerging techniques in patient motivation" looking specifically at motivation in rehabilitation.

Motivation in Rehabilitation

There are many challenges throughout the rehabilitation journey, and for patients perhaps one of the biggest challenges is ensuring the rehabilitation process is sufficiently stimulating, helping them to maintain a positive outlook. One approach is to have ongoing support from the likes of a professional trainer, who can also act as a "buddy", or as the renowned journalist, Andrew Marr once said, "a wise bully", when referring to his professional trainer.

The introduction of electronic games as a rehabilitation aid is arguably one of the most significant advances in motivating the rehabilitation process. They have certainly helped to transform a process that has previously been regarded as dull and boring into an activity that people happily adhere to, both in the hospital and at home. What's more, the use of computer games supports another established motivational technique of 'practice and reward' and encourages goal setting.

Dr Aitken went on to talk about the importance of setting 'Smart' Goals i.e. goals that are specific, measurable, achievable, realistic, and time-framed, as such goals are often used to aid the coordination between a multidisciplinary rehabilitation team when developing a rehabilitation plan for the individual needs of patients. Those goals then become an essential part of the rehabilitation feedback loop which includes monitoring progress against; the goals, other patients, and the literature. Then, we need to look at and measure the outcome of the rehabilitation process which includes:

- Patient reported outcomes
- Clinical reported outcomes
- Patient experience

Real World Data – Supporting Rehabilitation Services

Capturing and recording outcome data to support rehabilitation services was the focus of the second presentation by Ravi Patel, from Document Capture Company (DCC). Ravi highlighted how measuring outcomes has greatly informed the commissioning of services and has encourage services to highlight their achievements. He also explained how, by automating collection of outcome data, using the likes of the Goal Attainment Scale (GAS) and the Therapy Outcome Measure (TOM), it is helping commissioners to monitor and evaluate the impact of rehabilitation services across the UK.

Innovation in New Technologies

To complete the first ever BSRM satellite symposium, Keith Foster, VP Scientific Affairs, Toxins, Syntaxin (an Ipsen Company) rounded off the innovation theme with a presentation that highlighted how, by developing a range of botulinum neurotoxins, it may be possible to relieve the suffering from highly debilitating conditions such as spasticity.

Keith explained that Syntaxin have an ambitious plan to produce new and enhanced Botulinum Neurotoxins (BoNTs) with multiple therapeutic applications and to develop new formulations and new toxins that will considerably expand the spectrum of clinical applications and better address patients' needs (See Figure 1).

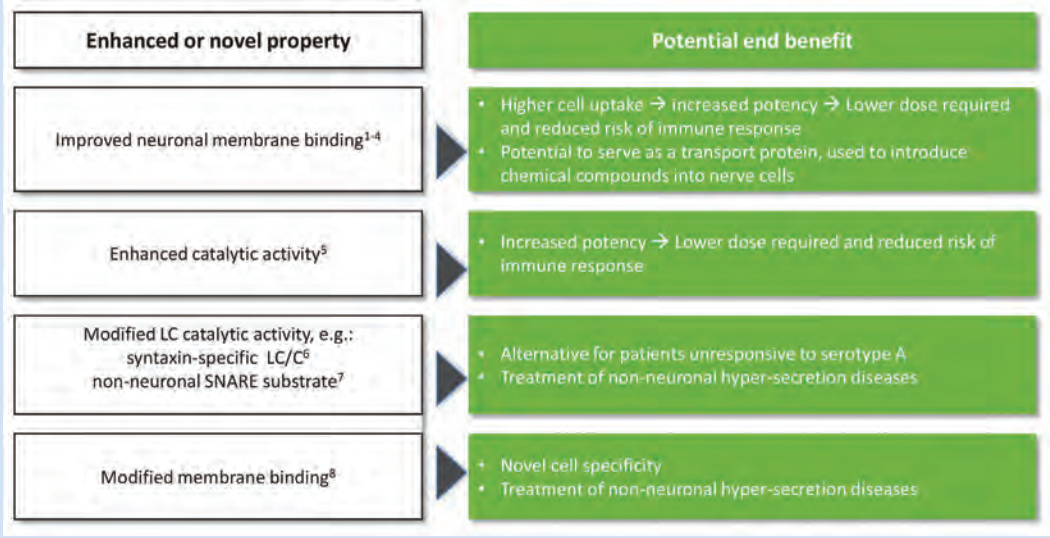


Figure 1 – Innovation in new technologies.

References

1. Rummel A, et al. FEBS J 2011; 278:4506-15.
2. Wang J, et al. Biochem J 2012; 444:59-67.
3. US Patent Application 20070299008; Kind Code A1; Rummel, Andreas; December 27, 2007. Transport Protein Which Is Used To Introduce Chemical Compounds Into Nerve Cells. [www.formulascan.com/public/appl20070299008.html].
4. Rummel A, et al. Toxicon 2013; 68:122-3. [Abstract].
5. Guo J, et al. Toxicon 2013; 74:158-66.
6. Wang D, et al. Biochem 2011;50: 2711-13.
7. Chen S, Barbieri JT. Proc Natl Acad Sci 2009;106: 9180-84.
8. Stancombe PR, et al. FEBS J 2012;279: 515-23.

Ipsen organised and funded this symposium and has funded the preparation of this Highlights report. Ipsen has had no editorial input into this item other than to check accuracy of claims.

December 2014 UK/DYS08882v(1)

The VIIth Practical Cognition Course

Course details: Thursday 25th and Friday 26th September 2014, Oxford, UK ***Report by:*** Dr Matthew Harris, Specialist Registrar in Neurology, Southampton General Hospital.

Have you ever thought that your assessment of patients with cognitive impairment could be improved, wondered how to interpret neuropsychological testing, or wanted to explore the beer cellars of Trinity College? Well the VIIth practical cognition course delivered on all of these and far more in a thought provoking two days!

It was a cool, but refreshing September morning. As I buttoned up my coat to shield me from the icy breeze, I couldn't help but stop to take in the architecture and history around me as I walked up the road to St Anne's College. Once I arrived, the seminar room gradually filled to near capacity with a varied audience of delegates from neurology, geriatrics, psychiatry, psychology and speech and language therapy.

Following a brief introduction from Tim Griffiths, the course got underway with Chris Butler talking through "what neurologists do in the cognitive clinic" covering key aspects of the history and examination. In the second talk Andrew Larner discussed the merits of various different cognitive instruments and guided us through the evidence for using these. Not too surprisingly the Adenbrooke's cognitive examination came out the most sensitive and specific, justifying those extra minutes required to complete it in clinic. Tom Kelly next gave an insight into the neuropsychological evaluation of patients with cognitive impairment with some humorous examples along the way.

After the initial lectures, the scene was set, and our minds were tuned into the cognitive wavelength. Chris Butler then proceeded to chair the discussions of cases of memory disorders. Each example generated interest from the audience, as well as the opportunity to interpret the neuropsychological evaluations and understand their results. One learning point that I took from this session was that impaired categorical compared to letter fluency can be an early sign in Alzheimer's disease indicating a breakdown in semantic knowledge.

Despite a hearty breakfast that morning, the morning's activity had left my stomach rumbling. Fortunately we were treated to an inviting spread of hot food, cold meats and salads to keep any hungry delegate going for the rest of the day. And if that wasn't enough, for dessert there were possibly the largest slices of chocolate cake I think I have ever seen – naturally I shared this with one of my fellow delegates!

After lunch the inevitable postprandial dip approached. Fortunately the afternoon started with a fascinating talk from Sinéad Mullaly on "what does the hippocampus do?" and my attention was held throughout. She discussed the current competing theories of memory consolidation and also shared some of her very interesting research on the role of the hippocampus in imagination and spatial visualisation.

The day continued with case discussions on sleep disorders. We heard of a case, referred to the cognitive clinic, in whom a sleep study proved much more useful than an MRI scan; listened to the bizarre behaviours that can occur in non-REM parasomnias, and pondered a challenging case of hypersomnia and amnesia.

Mid afternoon there was disappointment amongst the Neurologists and Psychologists in the audience when they found out that "TEA" on the timetable was neither a talk on transient epileptic amnesia, nor on the Test of Everyday Attention; but in fact an opportunity to recharge before the last talk.

Although it was the end of the day and the final talk was on sleep disorders, there was no need for extra coffee to keep the audience awake as Kirstie Anderson delivered a very informative talk on sleep disorders and cognition. After discussing the anatomical models of sleep, she covered the functions of sleep and the effects of sleep deprivation. We also learnt of the wide ranging associations between abnormal sleep and many neurological and psychiatric disorders such as Alzheimer's disease, depression and schizophrenia.

At the end of an engaging day, everybody headed to Trinity College to unwind and sample what was on offer in the beer cellar. After a few drinks people headed for dinner in the grand dining hall where paintings of past greats on the wall kept a close eye on the behaviour of those sat below!

The morning of the second day began with a neuropsychology "show and tell". Delegates were able to look through and discuss the various different tests utilised in an assessment with the neuropsychologists on hand. It was also an opportunity to test each other and work out who had enjoyed a few too many beers and not enough sleep the night before!

Chris Butler next presented clinical cases of motivation and apathy. We discussed the wide differential for potential causes of apathy and heard how patients with Parkinson's disease can experience particular problems in this area. Following on, Masud Husain gave an insightful talk on apathy and disorders of motivation, and we heard of a fascinating case of a middle aged man with significant apathy that improved with treatment with the dopamine agonist ropinirole. We were all left walking to lunch wondering if some of our colleagues could benefit from a dose of ropinirole now and then!

The afternoon began with case discussions of movement disorders associated with abnormalities of cognition. This section highlighted how the neurological examination can occasionally be very informative in patients with cognitive complaints, typified by one patient who presented with progressive frontal dysfunction without any motor complaints but an obviously abnormal examination. A number of cases included videos which really helped highlight some of the subtle signs that can easily be missed if they are not looked for.

James Rowe finished the course with an excellent coverage of the presentations of PSP and CBD, consolidating on some of the earlier cases. We learnt how verbal fluency for the letter P can be particularly sensitive in differentiating between Parkinson's disease and PSP. More importantly however, he discussed the need for a multidisciplinary approach in managing patients with conditions such as PSP, and that although called "movements disorders", the motor symptoms are only a small part of what can be a disabling disease.

All that remained at the end of the day was for us to complete our feedback forms on what had been two very worthwhile days of learning that will certainly change my future practice. I particularly enjoyed the balance of lectures and case discussions that kept the course interesting and the audience engaged. The use of patient videos really helped illustrate some key learning points in what was overall a very practical and clinically relevant course. I would certainly recommend it to anyone who is considering going next year!

The next Practical Cognition Course takes place at the Research Beehive, University of Newcastle on the 1st and 2nd of October 2015.

After a few drinks people headed for dinner in the grand dining hall where paintings of past greats on the wall kept a close eye on the behaviour of those sat below!

14th Annual Neuroradiology and Functional Neuroanatomy course

Conference details: 7-10 April 2014; The Hospital for Neurology and Neurosurgery, Queen Square, London, UK ***Report by:*** Dr Chinar Osman, Neurology Registrar, Southampton General Hospital. ***Organisers:*** Professor Thomas Naidich (Neuroradiology Mount Sinai, New York), Professor Christopher Yeo (Behavioural Neuroscience, UCL) and Professor Tarek Yousry (Lysholm Department of Neuroradiology, Queen Square).

This four-day course required the attendees to familiarise themselves with functional anatomy, cytoarchitectonic organisation of the brain and its clinical relevance. Participants were able to apply the theoretical knowledge acquired and apply it to clinical practice through using interactive medical imaging and hands-on dissection workshops. The attendees were of varying expertise, with levels ranging from Neuroscientists, Neurosurgeons and Neuroradiologists to Neurology Trainees like myself. Therefore, the course design accommodated non-clinicians and clinicians alike and coupled neuroscience with clinical neurology.

I chose to attend this course of interactive lectures delivered by world-class experts at the start of my specialist training to enhance my understanding of functional neuroanatomy.

Course contents

The course opened with an interesting insight into the phylogenetic evolution of the brain in humanoids, architectonic organisation of the telencephalon, neuroimaging with pre- and postnatal development of the white matter. It explored the fundamental functions of the brain in more depth such as the neurosignalling association pathways using functional imaging and tractography. Key regions covered were the cerebellum, corpus callosum, basal ganglia, hippocampus, amygdala, limbic system, vestibular system, insular and visual cortex.

Interesting learning points included

- Approximately 20% of the population have bilateral symmetrical connections responsible for language (with women more likely to be in this group)
- The left arcuate fasiculus is larger than the right and therefore has a better chance of recovery following an insult.
- Being able to locate areas according to gyri for example Heschels Gyrus (Primary Auditory Cortex) located on the superior temporal gyrus.

Interactive components

The famous neuroanatomist Professor Naidich delivered interactive sessions with participants shouting key landmarks of the gyri and sulci and demonstrated how we could use our hands to make signs which guided us in recognition of key landmarks. His key landmark was the sylvian fissure and from there we could locate neighbouring structures. This required complete participation and was the most I had ever engaged in a course as it used different aids to help us recognise various structures. For instance demonstrating to us where the central sulcus is located and how it divides the frontal lobe from the parietal lobe on different planes on MRI.

We had anatomy workshop demonstrations, located at a nearby university, with specimen reviews and dissections in small groups. It was led by Professors Naidich and Yeo. This complemented the previous lectures and started with surface anatomy, identification of important landmarks i.e. sylvian fissure and proceeded on to discovering and locating deep brain structures in various different planes. The workshops were a fantastic opportunity to gain practical experience with dissected human brain sections and we had to identify key areas using information given in the earlier lectures.

The sessions that I had found most clinically relevant were the small group imaging sessions where we had to locate different brain regions systematically and identify the abnormality and its clinical relevance under the supervision of neuroradiologists. A mixture of pathologies were presented, ranging from tumours and stroke to neuromigrational abnormalities.

Summary

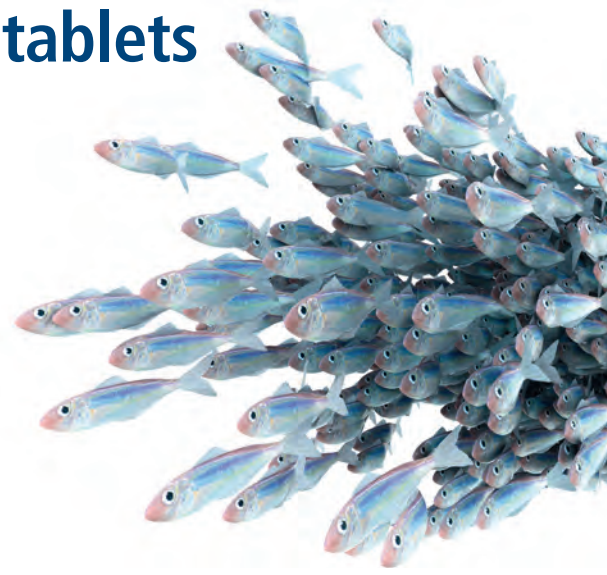
In summary this course is highly recommended for the neuroanatomy naïve professionals who require a working knowledge of neuroanatomy and an understanding of the relative functional and radiological significance of key brain regions.

The course was well organised, interactive and practical. It highlighted the research advances involved in improving our understanding of function, associating pathways and the clinical significance of key brain regions.

The 15th Annual Neuroradiology and Functional Neuroanatomy course takes place from the 23rd – 26th March 2015

DESITIN
SUCCESS IN CNS

The DoH Commercial Medicines Unit (CMU) awards **Desitrend®** as the chosen brand alternative to **levetiracetam oral tablets** in the national contract*



Desitrend®

levetiracetam 250mg, 500mg and 1000mg in UNIDOSE sachets

Epilepsy therapy in an intelligent form

The Desitrend® form of oral levetiracetam comprises granules in sachets. The award provides scope for you to prescribe Desitrend® as the chosen alternative to levetiracetam oral tablets if preferred.

Please write 'Desitrend®' or 'levetiracetam granules (Desitin)' when prescribing.

Contract duration: 1st November 2014 – 28th February 2017.

**With the permission of the Commercial Medicines Unit.*

Desitrend® (levetiracetam) Abbreviated Prescribing Information. Prescribers should consult the Summary of Product Characteristics before prescribing Desitrend®. Levetiracetam available as Desitrend® 250/500/1000 mg coated granules in sachet. Indications: Monotherapy of partial seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy of partial seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy. Adjunctive therapy of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. Adjunctive therapy of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. **Dosage and Administration:** *Monotherapy:* Adults and adolescents ≥16 years: Starting dose 250 mg twice daily increasing to 500 mg twice daily after two weeks. Dose can be further increased if required by 250 mg twice daily every two weeks to a maximum of 1500 mg twice daily. *Adjunctive therapy:* Adults and adolescents (12 to 17 years) weighing ≥50 kg: Initial dose 500 mg twice daily. Dose can be increased, if necessary, up to 1500 mg twice daily. Dose changes made in 500 mg twice daily increases or decreases every two to four weeks. Take orally, swallowed with a sufficient quantity of liquid, with or without food. Daily dose in two equally divided doses. Elderly: Adjust dose in renal impairment. Renal impairment: Adjust dose according to renal function. Hepatic impairment: severe impairment reduce daily maintenance dose by 50% when CLcr <60 ml/min. Children: Prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. Coated granules not adapted for use in children under 6 years. Available dose strengths not appropriate for initial treatment in children weighing less than 25 kg or for doses below 250 mg. Monotherapy: No data in children and adolescents below 16 years. Adjunctive therapy: Infants from 6 months, children and adolescents weighing less than 50 kg: Oral solution preferred formulation in children under 6 years. Initial dose 10 mg/kg daily. Dose can be increased if required up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. Use lowest effective dose. Dose in children ≥50 kg same as adults. Infants from 1 month to <6 months: use oral solution. **Contraindications:** Hypersensitivity to levetiracetam, to other pyrrolidone derivatives or to any of the excipients. Infants and children under the age of 6 years (levetiracetam oral solution is the preferred formulation for use). **Special warnings and precautions for use:** Patients with renal or severe hepatic dysfunction may require dose adjustment. Discontinue gradually (see SmPC). Although available data in children do not suggest impact on growth and puberty, long term effects remain unknown. The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. Patients should be monitored for respective signs and appropriate treatment should be considered. **Effects on ability to drive and use machines:** Reaction time may be impaired. **Pregnancy/lactation:** A teratogenic risk cannot be completely excluded. Use during pregnancy, lactation and in women of childbearing potential without contraception is not recommended unless clearly necessary. Levetiracetam plasma levels decrease during pregnancy, particularly in the third trimester. **Side effects:** *Very common:* Nasopharyngitis, somnolence, headache. *Common:* convulsion, dizziness, vertigo, lethargy, tremor, impaired balance, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, anorexia (increased risk when coadministered with topiramate), rash, cough, asthenia/fatigue. *Uncommon:* thrombocyto-/leucopenia, weight increase or decrease, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional lability/mood swings, agitation, amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention, diplopia, blurred vision, abnormal liver function test, alopecia (in several cases recovery of hair loss was observed after discontinuation of levetiracetam), eczema, pruritus, muscular weakness, myalgia, injury. *Rare:* infection, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, pancreatitis, hepatic failure, hepatitis, neutro-, pancytopenia (bone marrow suppression identified in some of the cases), agranulocytosis, DRESS, hyponatraemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme. Side effects occurring more frequently than in other age groups: children and adolescents between 4 and 16 years: *Very common:* vomiting. *Common:* agitation, emotional lability, mood swings, aggression, abnormal behaviour, lethargy. Infants and children between 1 month and 4 years of age: *Very common:* irritability. *Common:* coordination abnormal. **Pack sizes and NHS price:** Packs of 60, 250 mg sachets £22.41 [PL14040/0029]; Packs of 60, 500 mg sachets £39.46 [PL14040/0030]; Packs of 60, 1000 mg sachets £76.27 [PL14040/0032]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany. **Prepared in:** June 2014. For further information on Desitrend® please contact Medical Information on MedInfo@desitin.co.uk.

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 Desitin Pharma Limited on MedInfo@desitin.co.uk.

UK/DD/14/0007 Date of preparation: August 2014.