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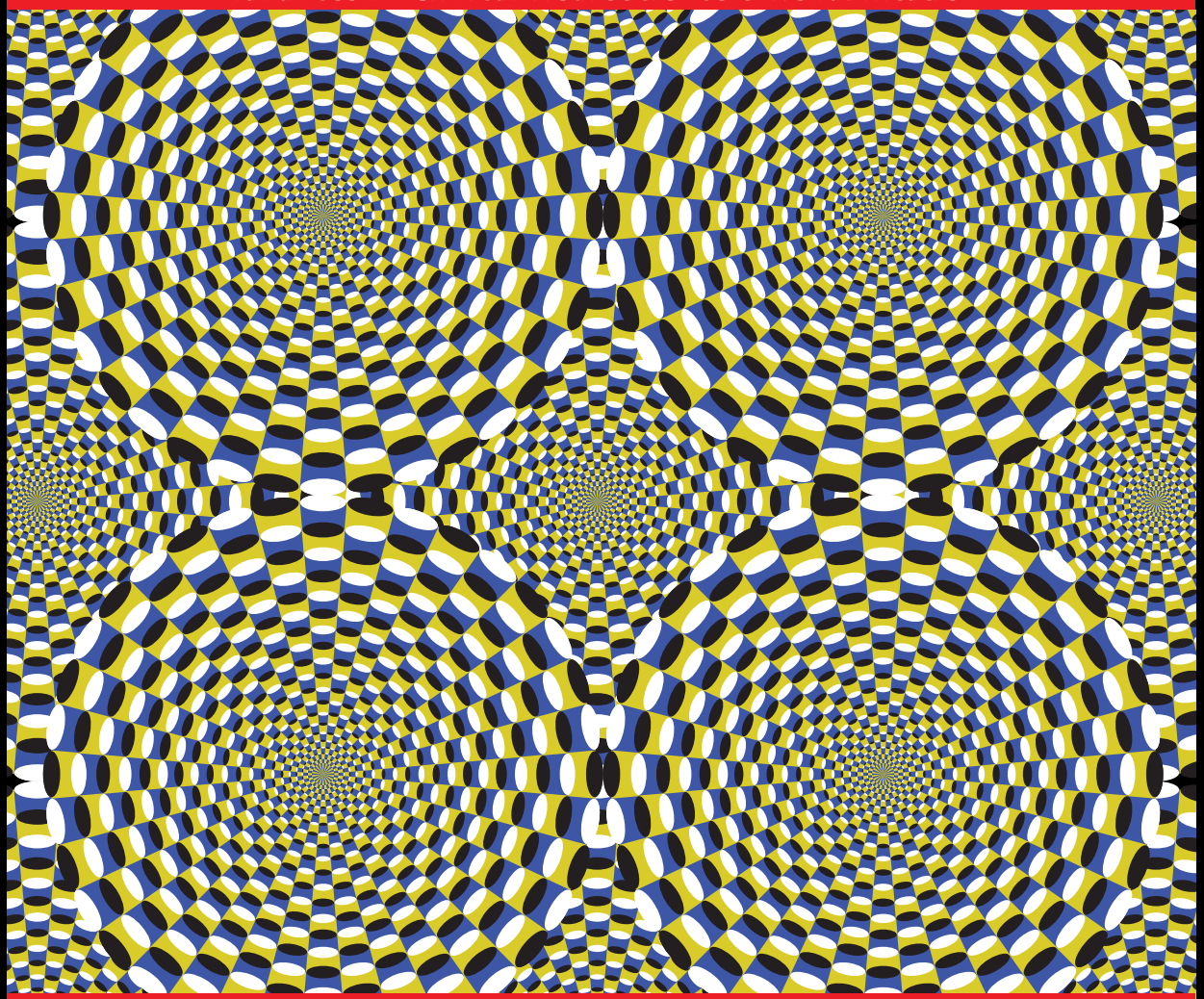
ACNR

Advances in Clinical Neuroscience & Rehabilitation



Conference News • Journal Reviews • Diary of Events • News Update

Mark J Edwards
DYT1 Dystonia

Gabriela Scheler et al
Significance of MEG in Presurgical Epilepsy Evaluation

Michael Hastings and Liz Maywood
The Circadian Clock and its Genes: in the Brain and Beyond

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Editorial Board and contributors

Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR. He has recently been appointed to the new position of University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Reader in Movement Disorder Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He runs Movement Disorders clinics in Newcastle upon Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

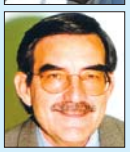
Alastair Wilkins is our Case Report Co-ordinator. He is Specialist Registrar in Neurology in Cambridge. His main research interests are the study of axon loss in multiple sclerosis and the molecular biology of axon-glia interactions in the central nervous system.

Roy O Weller is ACNR's Neuropathology Editor. He is Emeritus Professor of Neuropathology, University of Southampton. His particular research interests are in the pathogenesis of Multiple Sclerosis, Alzheimer's disease and Cerebral Amyloid Angiopathy.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital, Torino, Italy. President of the Italian Association of Neuro-Oncology, member of the Panel of Neuro-Oncology of the EFNS and EORTC Brain Tumour Group, and Founding member of the EANO (European Association for Neuro-Oncology).

Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ulrasound in Medicine, and the ENS.



Professor Hermann Stefan, Germany: Professor of Neurology / Epileptology in the Department of Neurology, University Erlangen-Nürnberg, andspecialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital. Research Dean at the medical faculty, and Chairman for the Research Committee of the Norwegian Medical Association. He chairs the scientist panel of neuroimmunology, EFNS, is a member of the EFNS scientific committee, the World Federation of Neurorehabilitation council, and the European School of Neuroimmunology board. His main research interests are neuroimmunology and neurorehabilitation.

First of all many congratulations to Rachael Hansford on the safe delivery of her first child, Charlie. Rachael (as many of you will not know) is the person who devised the ACNR, chases up all the articles, sorts out the structure of each issue and is the mastermind behind each issue. We hope she has a restful maternity leave and spends time looking after her most important baby, whilst we also extend a welcome and thanks to Patricia McDonnell for stepping into the breach.

Mark Edwards completed his research at the Institute of Neurology in London studying DYT1 dystonia. In his article he details the nature of this mutation, including a discussion on its cellular and clinical consequences, and highlights the pathophysiology that underlies this condition. In particular he highlights the fact that the failure to present before the age of 25 means that it is extremely unlikely that the individual will go on to develop dystonia despite carrying the mutation. This is a beautifully written article from someone who has provided intriguing new insights into this condition.

The review article by Scheler et al explains MEG and its value in the localisation of foci of epileptic activity, especially in cases where surgical resection is being considered. This is a difficult area of epilepsy management, as not only does one have to have accurate localisation of the epileptogenic focus but also one has to ensure that its removal does not induce any significant new deficits. The non invasive technique of MEG, according to the authors, is more sensitive than scalp EEG but, not surprisingly, is less good than intracranial EEGs in terms of localising the source of epileptic seizures. As a result it can help in the decision making process in the presurgical evaluation of patients with epilepsy in a significant proportion (approximately 10%) of cases.

Understanding circadian rhythms is an area of intense biological and clinical interest and we are thus very fortunate to have a review by Mick Hastings and Liz Maywood, two leading researchers in this area. Their article provides us with a wonderful example of 'genes-to-cells-to-behaviour' and discusses how the suprachiasmatic nucleus of the hypothalamus co-ordinates a number of local clockworks in different organ systems, and how this can go wrong with neurological disease. This is a beautifully clear account, which summarises a fascinating topic and includes up-to-date studies from the authors themselves.

The article in the excellent series on visual neuroscience (edited by Masud Hussain) is by Bach and Poloschek and treats us to some rather mindchurning optical illusions. This article presents a plethora of images, many of which can leave one feeling slightly spaced out and nauseated. However the authors argue that optical illusions, whilst being entertaining, can also inform us on mechanisms of visual processing as well as aspects of visual perception.

The neuropathology series heads to the peripheral nervous system, where Roz King takes us through the normal structure of nerves to pathology and the features distinguishing demyelinating from axonal neuropathies. The article contains some extremely helpful tables as well as summarising the indications, methods and analysis of a nerve biopsy, with helpful comments on the distinguishing pathology of the different aetiological causes of neuropathy. As with all articles in this series, it is beautifully illustrated, succinct and combines scientific excellence with pragmatism.

Rehabilitation following traumatic brain injury (TBI) is a common scenario and Helen Seeley and Peter Hutchinson take us on a sobering tour of this area, highlighting the dearth of facilities available for delivering such a service. This in part relates to ignorance as to its worth, and the need to develop a team of co-ordinated and dedicated specialists. The authors, who work in the Eastern region, have therefore used this area to investigate the nature of the problems associated with differing types of TBI and how they can best be tackled at a network level. This raises many issues, not least the cost implications that any such services would impose on the NHS, which in turn has consequences for their national adoption.

"Orthoses are external devices designed to affect body function and/or assist function" so write David Abankwa and Alan Llewellyn in their article on the use of such devices in the management of lower limb spasticity. This nicely illustrated account may cover familiar ground to those involved in rehabilitation, but will certainly be an eye-opener to those working outside this discipline but who nevertheless see such patients.

In Drugs in Neurology, Donald Grossett in a sponsored article discusses rotigotine, which is the first dopamine agonist to be delivered successfully by transdermal application. This drug thus offers a new option for patients with early-stage Parkinson's disease as it may produce less pulsatile stimulation of dopaminergic receptors, which may have implications in the genesis in the long term of drug induced dyskinesias.

Andrew Larner in his second treatise on headache in literature concentrates on the work of Ian McEwan as well as Jack London, whilst also exploring the different types of headaches exhibited by the Little Women of Louisa M Alcott. As always with Andrew, the article is beautifully constructed and thought-provoking.

We have our usual journal, conference and book reviews, and don't forget the website where you can freely download any of the articles from the ACNR.

Roger Barker, Co-Editor, Email: roger@acnr.co.uk

Journal reviewers this issue:

Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Roger Barker, Cambridge Centre for Brain Repair;
Alasdair Coles, Cambridge University;
Andrew Larner, Walton Centre, Liverpool;
Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;
Wendy Phillips, Addenbrooke's Hospital, Cambridge;
Robert Redfern, Morriston Hospital, Swansea;
Ailie Turton, Burden Neurological Institute, Bristol.

Would you like to receive a subscription to **Clinical Rehabilitation** in return for providing reviews for ACNR? For more information email patriciamcdonnell@btinternet.com or telephone on 0288 289 7023.

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Now for adjunctive treatment of partial onset seizures in adults and children from 4 years of age.

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ABBREVIATED PRESCRIBING INFORMATION
KEPPRA® film-coated tablets 250 mg, 500 mg, 750 mg, 1000 mg
KEPPRA® 100 mg/ml oral solution
Consult summary of product characteristics (SPC) before prescribing.
Active Ingredient: *Tablets:* levetiracetam 250, 500, 750 and 1,000 mg. *Solution:* levetiracetam 100 mg per ml. **Uses:** Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age. **Dosage and administration:** Oral solution should be diluted prior to use. *Adults and adolescents older than 12 years of 50 kg or more:* 500 mg twice daily can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg:* 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations for children, adolescents and adults see SPC.) *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the oral solution may cause allergic reactions (possibly delayed). **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, agitation, personality disorders, thinking abnormal, vertigo, rash, diplopia, infection, cough increased. Consult SPC in relation to other side effects. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. Solution x 300ml: EU/1/146/027. **NHS price:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. Solution x 300ml: £71.00. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. medicalinformationuk@ucb-group.com **Date of revision:** December 2005

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to UCB Pharma Ltd.

References:
1. Krakow K, Walker M, Otoul C, *et al.* Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology.* 2001; 56: 1772-1774. **2.** Glauser TA, Gauer LJ, Lu Z, *et al.* Poster presented at IEC, Paris, 2005. **3.** Keppra, Summary of Product Characteristics, September 2005. **4.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001; 47: 77-90. **5.** Glauser TA, Gauer LJ, Chen L, *et al. Epilepsia* 2004; 45: 186. **6.** Data on file, UCB Pharma.

* Includes patients of all age groups.

Printed in the UK
Date of preparation: March 2006.
06KP0061

ucb CNS INNOVATORS™

MIRAPEXIN: New indication for moderate to severe RESTLESS LEGS SYNDROME

Prescribing Information RLS UK
Mirapexin™ (pramipexole) Presentation: Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing **0.125mg, 0.25mg** and **1.0mg** respectively of pramipexole dihydrochloride monohydrate. **Indications:** Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS). **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water 2-3 hours before bedtime. Start with 0.125mg salt (0.088mg base). This dose may be increased every 4-7 days to a maximum of 0.75mg salt (0.54mg base). Re-evaluate after 3 months. Renal impairment: Patients with creatinine clearance above 20mL/min require no reduction in daily dose. Hepatic impairment: Dose adjustment in hepatic failure is not required. Children: No data in patients under 18 years. **Contra-indications:** Hypersensitivity to pramipexole or any other constituent. **Warnings and Precautions:** Inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machines. (A reduction of dosage or termination of therapy may be considered). Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. Literature indicates possibility of augmentation. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. Pramipexole should not be used during breast-feeding. **Undesirable Effects:** The most commonly reported adverse reactions in patients with RLS were nausea, headache and fatigue. Women reported 20.8% nausea, 10.5% fatigue and men 6.7% nausea, 7.3% fatigue. Frequency of adverse reactions collected from experience in Parkinson's disease and RLS includes; very common - nausea 17.2% and dyskinesia 12.9%, and common -somnolence 8.6%, insomnia 8.0%, headache 6.5%, fatigue 6.1%, constipation 5.5%, visual hallucination 4.6%, confusional state 3.0%, hallucination 2.0%, and peripheral oedema 1.2%. Sudden sleep onset 0.1%, libido increased 0.1%, libido decreased 0.4% and dizziness. The majority of common adverse reactions were mild to moderate, usually started early in therapy, and most tended to disappear even as therapy continued. Hypotension may occur at the beginning of treatment, especially if Mirapexin is titrated too fast. Pathological gambling, especially at high doses seen in Parkinson's disease, generally reversible upon treatment discontinuation. For full details of these and other side effects, please see the Summary of Product Characteristics. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse reactions include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring. **Basic NHS Cost:** 0.125mg (0.088mg) x 30 £9.25, 0.25mg (0.18mg) x 30 £18.50, 0.25mg (0.18mg) x 100 £61.67, 1.0mg (0.7mg) x 30 £58.89, 1.0mg (0.7mg) x 100 £196.32. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg (**0.125mg**) x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg (**0.25mg**) x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg (**0.25mg**) x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg (**1.0mg**) x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg (**1.0mg**) x 100 tablets EU/1/97/051/006. Further information is available from Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** April 2006.

Adverse events should be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Information about adverse event reporting can be found at www.yellowcard.gov.uk

References:
1. Oertel W, Stiasny-Kolster K *Movement Disorders* 2005; **20**(10): S58 Abstr P194. **2.** Partinen M *et al. Neurology* 2004; **63:** 1545 Abstr LBS.002. **3.** Winkelman J *et al.* Poster and abstract presented at 58th Ann Mtg of Am Acad of Neurol (AAN) 2006 San Diego: P02.022. **4.** Leissner L *et al. European Journal of Neurology* 2005; **12**(2): 217 Abstr P2207.

Boehringer Ingelheim

RLS 0212

Mirapexin delivers rapid[1] and effective relief from a broad range of symptoms of RLS with a starting dose of 0.125mg once daily[2-4]

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pramipexole

Relieve the distress of RLS

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Aricept®

donepezil hydrochloride

Continuing Commitment To Alzheimer's

ABBREVIATED PRESCRIBING INFORMATION
ARICEPT® (donepezil hydrochloride)
Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** Pregnancy. Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Lactation:** Excretion into breast milk unknown. Women on donepezil should not breastfeed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures – in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £63.54. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM. **Date of preparation:** November 2005.

Information about adverse event reporting can be found at www.yellowcard.gov.uk
Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or Lmedinfo@eisai.net

Eisai Pfizer NEUROLOGY

Date of preparation: November 2005. A892e-ARI779i

Contents

May/June 2006

Erratum: Please note that the title and page number of the Neuropathology article in Volume 6 issue 1 of ACNR (March/April 2006) should have read as follows:
14 The Clinical Pathology of Muscle Disease, Dr Leslie R Bridges.
We apologise for any inconvenience caused by this error.

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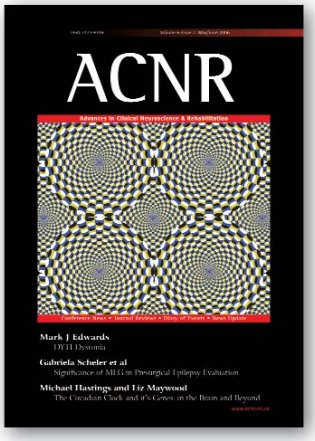

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Each disk appears to expand.

More out of levodopa.
More out of life.

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STALEVO (levodopa / carbidopa / entacapone)
PRESCRIBING INFORMATION
Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration:** Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. *Children and adolescents:* Not recommended. *Elderly:* No dosage adjustment required. *Mild to moderate hepatic impairment, severe renal impairment (including dialysis):* Caution advised. **Contraindications:** Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions:** Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** *Levodopa / carbidopa* — Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. *Entacapone* — Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and marketing authorization numbers:** Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/002-003; Stalevo 100mg/25mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/006-007; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40 MA numbers: EU/1/03/260/010-011. **Distributed by:** Orion Pharma (UK) Ltd., Oaklea Court, 22 Park Street, Newbury, Berkshire, RG14 1EA, UK. Full prescribing information is available on request. Stalevo is a registered trademark. **Date of Prescribing Information:** December 2005.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Orion Pharma (UK) Ltd on 01635 520300.

ORION PHARMA

Item Date: January 2006
STA2243

DYT1 Dystonia

Primary Young-onset Dystonia and the DYT1 mutation

Primary dystonia is defined as the presence of dystonia as the only symptom (with or without tremor), with no clear secondary cause and no neurodegeneration. Patients with primary dystonia with onset before the age of 25 tend to develop limb dystonia which often generalises, but tends to spare the head and neck. This pattern has been referred to by many names over the years: primary torsion dystonia, dystonia musculorum deformans, Oppenheim's dystonia. In 1997, Ozelius and colleagues identified a mutation in the DYT1 gene on chromosome 9q in about 70% of patients with this young-onset primary dystonia phenotype. [1]

The DYT1 Mutation and its cellular consequences

The DYT1 mutation is a single GAG deletion that causes the loss of a glycine residue close to the ATP-binding end of the protein torsin A.[1]

The function of torsin A is unknown. It is widely expressed throughout the body and in the brain is mainly localised to the dopaminergic neurons of the substantia nigra, and also the hippocampus.[2] Torsin A is an endoplasmic reticulum-bound protein[3] and forms part of the AAA+ superfamily of ATPases (ATPases with A variety of cellular Activities). Torsin A is hypothesised to form a six membered ring structure, and may serve a chaperone function, for example in the folding or unfolding of proteins,[4] perhaps including those involved in dopamine release from vesicles.[5] Over-expression of wild-type torsin A appears to protect cultured cells from toxic insults. As in vivo evidence of this cellular protection function, torsin A has been identified as a component of Lewy bodies.[6]

When mutant torsin A is over-expressed in cell cultures, inclusion bodies form within the cells consisting of 'whorls' of mutant protein.[7] Pathological studies of the brains of those with DYT1 dystonia are in general normal,[8] but inclusion bodies within cholinergic neurons in the brainstem of DYT1 mutation carriers have recently been reported.[9]

DYT1 Dystonia: Inheritance and Phenotype

DYT1 dystonia is inherited in an autosomal dominant fashion, but with markedly reduced penetrance. Only 30-40% of mutation carriers ever develop dystonia, and in those that do, almost all develop symptoms before the age of 25.[10]

Typical age at onset is in late childhood or early-teens. Dystonia almost always starts in a limb, and then spreads to affect other limbs. The head, neck and bulbar structures are rarely affected. The degree of eventual spread is very variable between patients, ranging from isolated hand dystonia to severe generalised dystonia.[10 11]

Spread of symptoms usually occurs over two to four years after onset, and then symptoms will stabilise. Minor fluctuations of symptom severity may then occur, and secondary problems (eg. scoliosis) may develop later, but late-development of dystonia in a previously unaffected body part is rare.[10]

The differential diagnosis in DYT1 dystonia is not usually extensive. Most patients with secondary/heredodegenerative dystonia will have other symptoms and signs apart from dystonia, or the dystonia will be of a pattern that would be unusual for primary young-onset dystonia (eg. cranial/bulbar involvement). Of course, such additional symptoms and signs may not be present at the onset of the dystonia. Two important differentials in this regard are dopa-responsive dystonia and young-onset Parkinson's disease. It is also important to remember that the DYT1 mutation only accounts for a proportion of those with the 'Oppenheim dystonia' phenotype, and there are a number of patients who are DYT1 negative, but nevertheless have a typical DYT1 phenotype.

The pathophysiology of DYT1 dystonia

Electrophysiological and functional imaging investigation of those with DYT1 dystonia has identified a number of deficits in inhibitory motor pathways in the brain, brainstem and spinal cord.[12 13] These are similar to the abnormalities found in patients with other forms of primary dystonia (eg. torticollis).[14] Interestingly, similar abnormalities of cortical motor function are found in carriers of the DYT1 mutation who do not have dystonia.[12] Such abnormalities are therefore not sufficient on their own to cause dystonia. There is increasing interest in the idea that an excessive ability to undergo plastic change in the motor system may underlie the development of primary dystonia in general. There is some limited evidence that this may also be the case for DYT1 mutation carriers who manifest dystonia, but that carriers without dystonia may have less ability to undergo plastic change than normal subjects.

Guidelines for Diagnostic Testing

Diagnostic testing guidelines have been published for DYT1 dystonia.[10] It is suggested that diagnostic testing be performed in those with primary dystonia who have onset below the age of 26. Testing of those with onset after 26 is only recommended if there is a family history of typical young-onset primary dystonia. Gene testing is technically straight-forward, and is commercially available.

Treatment of DYT1 Dystonia

Until the advent of deep brain stimulation surgery (see

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DYT1 dystonia is inherited in an autosomal dominant fashion, but with markedly reduced penetrance. Only 30-40% of mutation carriers ever develop dystonia, and in those that do, almost all develop symptoms before the age of 25

below), the mainstay of treatment was with medication and in some cases botulinum toxin.

Most patients receive a trial of levodopa. This helps to exclude the possible diagnosis of dopa-responsive dystonia as the cause of the symptoms, and also, a small minority of patients with DYT1 dystonia can have a partial response to levodopa.

Anticholinergic drugs are still the mainstay of medical treatment for DYT1 dystonia. Trihexyphenydyl should be introduced very slowly. Patients should aim for the highest tolerated dose: young patients can sometimes reach very high doses (up to 100mg per day) with good benefit on symptoms if titration is slow. However, many patients reach the point of unacceptable side effects long before a useful impact on symptoms occurs.

Other medical treatments (often used in combination) include benzodiazepines (eg. clonazepam), tetrabenazine and baclofen. For severely affected patients, a popular strategy in the past has been to use a 'triple therapy' of anticholinergic, benzodiazepine and dopamine receptor blocking drugs.

Botulinum toxin injections have a limited role in those with DYT1 dystonia. If a particular functional problem can be identified (eg. dystonic spasm of the dominant hand causing inability to write), then treatment with botulinum toxin may be indicated. However, for those with generalised symptoms there are often too many muscles that require treatment for injections to be of benefit.

Lesion operations of the basal ganglia (eg. pallidotomy) were previously used in those with DYT1 dystonia, with some success, but also side effects. In recent years, deep brain stimulation of the internal segment of the globus pallidus (GPi), has emerged as a very promising therapeutic option for those with DYT1 dystonia. Improvement of dystonia of 70-95% is typical in those treated with GPi stimulation, and the improvement appears to be sustained (over at least five years of follow up so far).[15] The operation does carry acute (eg. haemorrhage) and long term (eg. lead infection, fracture) complications, but overall within a specialist centre, results are highly consistent.

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Significance of MEG in Presurgical Epilepsy Evaluation

Summary

Magnetoencephalography (MEG), as a non-invasive procedure, records magnetic fields generated by spontaneous or evoked brain activity. Presurgical evaluation of pharmacoresistent patients with focal epilepsy is currently the most frequent diagnostic application. The source of epileptic or averaged evoked activity is localised and then overlaid onto magnetic resonance imaging (MRI) of the patient's brain. For source localisation advanced techniques use information extracted from the individual brain. The localisation results can guide invasive recordings and help in neurosurgical operation planning. Owing to the physical constraints of MEG and EEG, source localisation can be improved by simultaneous recording. Together with other diagnostic methods, MEG plays an important role for focus localisation in patients with intractable epilepsy.

Introduction

In the last decade diagnostic techniques have improved and by so doing have allowed for a more individually tailored epilepsy surgery, such that it has has gained importance for patients with intractable epilepsy. The aim of presurgical evaluation is to identify the epileptogenic zone which is necessary and sufficient to control seizures when removed.[1,2] For this purpose, several diagnostic methods are applied: Electroencephalography (EEG), Magnetic Resonance Imaging (MRI), Positron-Emission-Tomography, Single-Photon-Emissions Tomography, Video-EEG-Monitoring, neuropsychological investigation and Magnetoencephalography (MEG). Among these methods, the significance of MEG is based on a high temporal and good spatial resolution which in turn allows for identification of functionally important areas relative to the epileptogenic region.

Data aquisition

MEG and EEG measure the electromagnetic signals of the brain, which are generated by the activity of cortical neurons. The magnetic field of the brain is extremely weak (10^{-12} to 10^{-15} Tesla) and thus much smaller than the ambient electromagnetic noise in the environment. The development of a superconducting quantum inference device (SQUID) allows the investigation of the brain's magnetic activity. A shielded room attenuates disturbance of the MEG recording by distant electromagnetic noise. The acquired data describe the change of the magnetic fields. In contrast to electric fields, magnetic fields are less distorted by the resistive properties of the skull and scalp. Electric and magnetic fields are oriented perpendicular, orientation of the highest sensitivity for EEG and MEG is orthogonal to each other. Therefore both non-invasive methods are complementary, the combination of both techniques yields information not available from either technique alone.[3]

Source localisation

The so-called neuromagnetic 'inverse problem' - the tracing of an unknown source in the brain from magnetic field data recorded outside the head – has no unique solution, additional constraints are necessary. An algorithm iteratively minimises the differences between the observed and the calculated field for a hypothetical source. For an estimated dipolar source, the magnetic fields in the sensors or the electric potential at the scalp can only be calculated, when the electromagnetic properties of the volume between are known. This description of the head's properties is called volume conductor, which is commonly based on individual anatomical structures. A volume conductor model, which resembles the electromagnetic properties of the head, is more difficult to obtain for EEG than for MEG.[4] This is because inhomogenities in conductivity hardly affect magnetic fields, but they considerably alter the way an electrical potential within the brain is transformed to the head surface.[5] The first and still widely used head model is a homogeneous and isotropic spherical head model. Boundary element methods can describe the surfaces of volumes with identical electromagnetic properties in the individual MRI.[3] The goal is to estimate the individual features as closely as possible, since any deviation between the actual and the assumed volume conductor might influence the results.[6]

The configuration of the source signal can also be approximated by a model. The single equivalent current dipole model has been used most frequently. However, when sources overlap both spatially and temporally (ie. in the case of multifocal sources) the approach of a multidipole source model might be more appropriate.[7] Furthermore, current density reconstruction methods without assumptions about the source signal are applied. This method searches for the minimum currents which can explain the measured field; they have been preferentially applied for a more extended generator.[8] All localisation results have to be understood as the centre of a confidence volume.

Figure 1a: Whole head system, VSM MedTech Ltd, Coquitlam, BC, Canada.

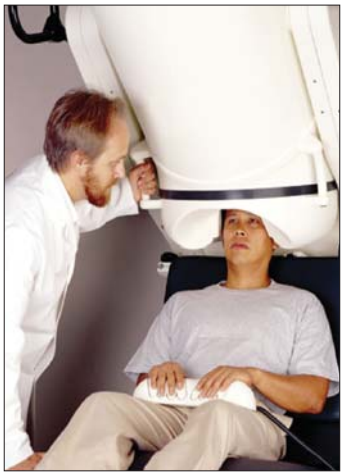

Figure 1b: Whole head system, 4D-Neuroimaging, San Diego, California, USA.

Gabriela Scheler is neuropsychologist and scientist at the Friedrich-Alexander-University of Erlangen-Nuremberg, Germany. She works in the MEG laboratory of the Epilepsy Center, investigating patients with intractable epilepsy. Her research aims to identify the region of the brain responsible for seizures and the pathophysiological basic principles.

Michael Fischer studied medicine at the University of Erlangen-Nuremberg. The research year in the MEG laboratory addressed the differences between source localisations in MEG versus EEG and the effect of different volume conductors. A further project deals with the generation of result volumes from single source localisations. The current research interest is focused on pain.

Hermann Stefan is Neurologist and Epileptologist. In his position as director of the Epilepsy Center at the Neurological Department of the University Clinic Erlangen, Germany, his work is concentrated on the investigation of epilepsies, their diagnostics, differential typology and therapeutic treatment. For this purpose he increased the diagnostic possibilities of clinical application and subsequently specialised in the preoperative diagnosis in patients with therapy resistent epilepsies.

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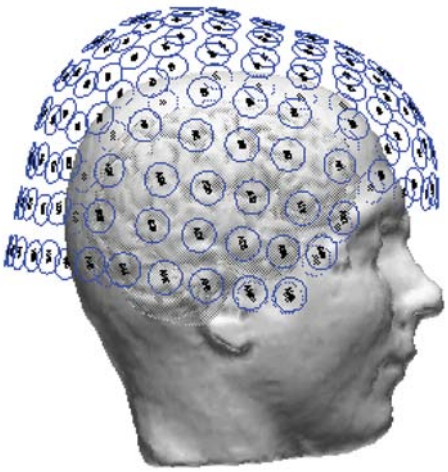
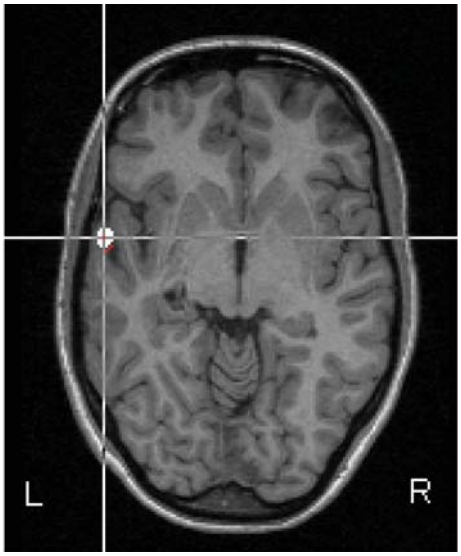


Figure 2: Sensorpositions of a 148-channel MEG-whole head system Magnes 2500 WH, visualised over a surface reconstruction of head and brain of a patient. Sensorposition data are courtesy of Prof Dr Angela D Friederici, MPI for Neuropsychology, Leipzig, Germany.



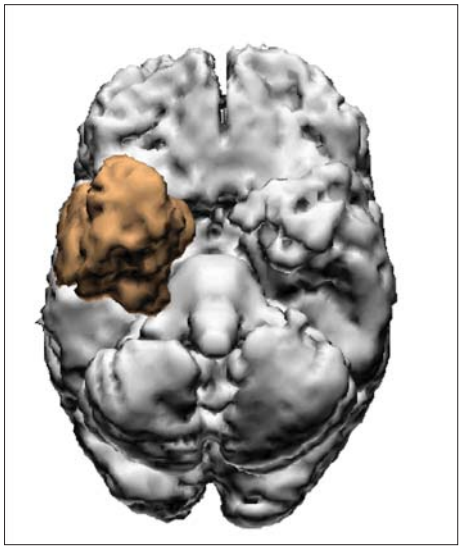


Figure 3: Patient with polymicrogyria in right temporal lobe. Outcome after resection: patient is seizure free.
Figure 3a: MEG localisation of the epileptiform focus (white).
Figure 3b: Segmentation of the resected part of the brain (black).

After coregistration of MEG and MRI data using a combined coordinate system, localisation results can be superimposed to individual brain anatomy (Magnetic Source Imaging, MSI). Source localisation of epileptic discharges can thus be attributed to specific brain structures.

Diagnostic yield

Magnetoencephalography (MEG) can contribute to the presurgical evaluation process. In a retrospective study interictal spikes were detected in 76% of 300 patients, the epileptic lobe was correctly identified in 89% of 455 cases and MEG yielded crucial information for decision making in 10% of these patients.[9] The contribution of MEG to the general result of presurgical evaluation was quantified in 104 patients. MEG supplied additional information in 35% and information crucial for the final decision in 10%. In a systematic study of 58 patients MEG performed better than both interictal (33%) and ictal (20%) scalp-EEG, but worse than interictal (75%) and ictal (81%) intracranial EEG.[10] MSI has also been found to offer useful source locations of cryptogenic epileptic activity in accordance with other non-invasive results. In 11 out of 12 patients without focal abnormality in MRI, MEG discharges were localised to the epileptogenic zone as determined by standard preoperative evaluation.[11] A good positive outcome was correlated with a high coverage of MEG results by the neurosurgical resection.[12] Review of MEG-localised epileptiform areas on high-spatial-resolution MR images can enable detection of epileptogenic neocortical lesions, some of which are occult on conventional MR images.[13]

In cases where neurosurgery remains the only therapeutic hope for epileptic patients, it is essential that not only the site of the epileptogenic region is known, but also to determine whether removal of the tissue in question may cause functional deficits. The localisation of primary sensory and essential secondary cortical areas are required to design neurosurgical strategies. Structural imaging fails to reliably identify functionally significant areas which may be displaced not only by tumors or oedema, but also by brain plasticity. However, MEG localisations of the primary somatosensory, auditory and visual cortices are performed routinely and have been used for preoperative planning as well as intraoperative neuronavigation.[14] Functional MEG localisations are particularly favourable in cases where the epileptogenic area is closely related to overlapping, eloquent regions.

The applications of MSI in presurgical epilepsy evaluation can be summarised as follows:

- Localisation of focal epileptic activity to guide invasive procedures and thus reduce invasive regimens
- Delineation of functionally significant areas (which must be spared in neurosurgery) by means of evoked activity
- Localisation of focal epileptic activity to guide detailed planning of neurosurgical procedures, eg. with neuronavigation, aiming at the removal of as little tissue as possible.

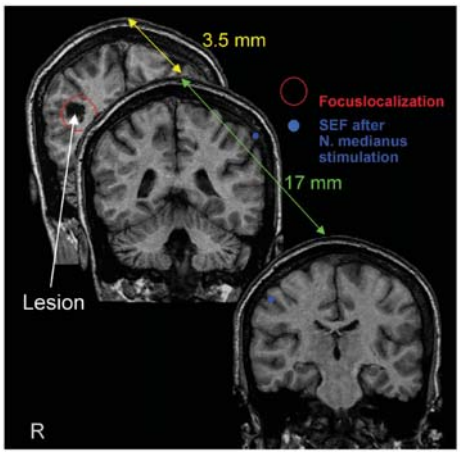


Figure 4: MEG localisation result at the border of the lesion (red). Somatosensory evoked fields (SEF) after median nerve stimulation. Reorganisation of the somatosensory representation on the side of a lesion in a frontal direction in a patient with symptomatic extratemporal epilepsy.

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The Pathology of Peripheral Nerve Diseases

Introduction

This article will first briefly summarise the structure of the normal peripheral nerve followed by a description of the changes seen when either the axon or the myelin degenerates. Then there is a summary of the clinical features of peripheral neuropathy and the means of investigating them. Next there is a short paragraph on performing the nerve biopsy and what information can be obtained from it. The features that can lead to a diagnosis will then be described. Hereditary neuropathies have attracted considerable interest recently so the article finishes with a very brief overview of the most important of these.

Nerve structure

A nerve trunk is composed of several fascicles; perhaps as many as 12 in a sural nerve (the most frequently biopsied nerve). Each fascicle is a cylindrical bundle of nerve fibres ranging in size from 0.1micron to 20 micra (Figure 1). Nerve axons are extensions of the cytoplasm in the cell body to form long nerve fibres whose function is to carry electrical signals from neurons in the brain to muscles and various types of sensory end organs. If these connections are damaged there are various adverse effects. For example, the patient may have numbness or painful sensations in the territory of the nerve that is damaged, or paralysis if a motor nerve is affected.

The smallest fibres, up to 2.5-3 micra in diameter, lie in small bundles in an ensheathing Schwann cell. These are axons carrying signals from endings sensitive to pain, and temperature to the brain. Fibres larger than 3 micra are normally surrounded by myelin. This is a lipid and protein lamellar structure produced by the Schwann cell when its axon signals it to do so. These larger axons are covered by a chain of Schwann cells each producing a myelin segment. These join at specialised structures called nodes of Ranvier. In unmyelinated nerves the impulses are conducted along the axon slowly in contrast to when the axon is coated with a myelin sheath, where the impulse jumps between nodes (saltatory nerve conduction) that can be as much as 1mm apart, thus greatly increasing the nerve conduction velocity. This is important for motor nerves where a quick reaction to an unpleasant stimulus may be vital. Although the myelin sheath has a beneficial effect on nerve function, it is more susceptible to damage by trauma and disease than unmyelinated axons. In addition the latter are not arranged in a 1:1 system with individual Schwann cells so if one Schwann cell is damaged another can replace it easily. Hence many nerves whose function is vital to survival are small and unmyelinated.

Pathology of peripheral nerves

The composition of nerve trunks means that any of the components, axons, myelin, Schwann cells or blood vessels may be the primary target of disease or injury (Table 1). There may also be a secondary effect on the nerves of a systemic metabolic disease. The effects of these various insults will be seen on the nerve biopsy as demyelination and remyelination and/or axonal degeneration and regeneration.

Demyelination

Demyelination is characterised by loss of myelin along one or more segments of a fibre without necessarily affecting adjoining ones. The process of demyelination is usually very rapid and the degenerating myelin commonly shows as small balls of myelin breakdown products in the Schwann cell cytoplasm alongside an axon lacking a myelin sheath. During recovery Schwann cells multiply and spread along the denuded region of the axon before making a new myelin sheath. If the process is repeated, excess Schwann cells may be produced. These then encircle the remyelinating fibre and may be so extensive that the nerve is enlarged and palpable through the skin. They are called (classical) onion bulbs, when they are composed of layers of Schwann cell processes, and basal laminal onion bulbs when the Schwann cell processes have retracted leaving only layers of basal lam-

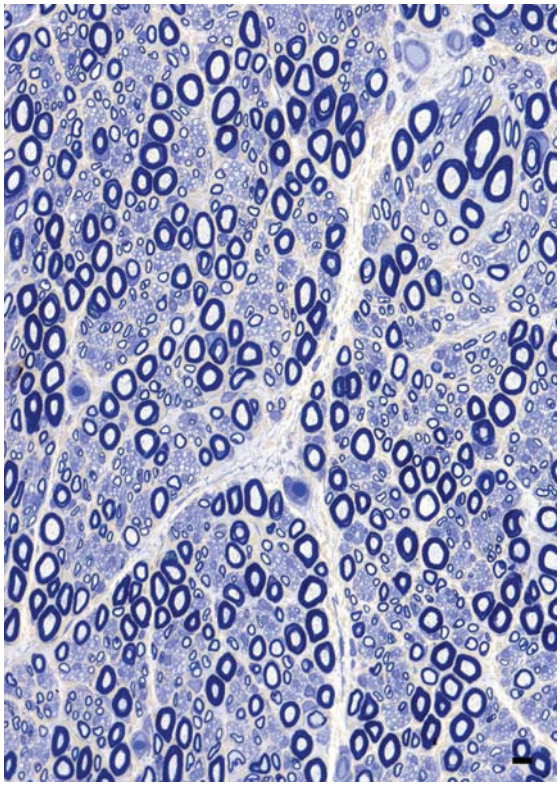

Figure 1: Normal human sural nerve showing the range and density of myelinated fibre sizes. Bar = 10μm.

Table 1. Main causes of peripheral neuropathy:

Neuronopathy	*Spinal Muscular Atrophy (SMA)* *Sjögren's Syndrome* *Herpes zoster* *Carcinomatous sensory ganglionopathy*
Axonopathy	*Diabetes* *Vasculitis* *Uraemia* *Trauma* *Drug toxicity* *Autoimmune axonal neuropathies* *Amyloidosis* *Hypothyroidism* *Alcohol* *Hereditary axonal neuropathies (CMT 2, SMA etc)* *Leprous neuritis* *POEMS*
Demyelination	*Autoimmune demyelination(GBS, CIDP)* *Hereditary demyelination (CMT1, HNPP, Metachromatic Leukodystrophy etc)* *Paraproteinaemic neuropathy* *Leprosy* *Diphtheritic neuropathy* *Lymphomatous neuropathy* *Secondary to axonal atrophy*

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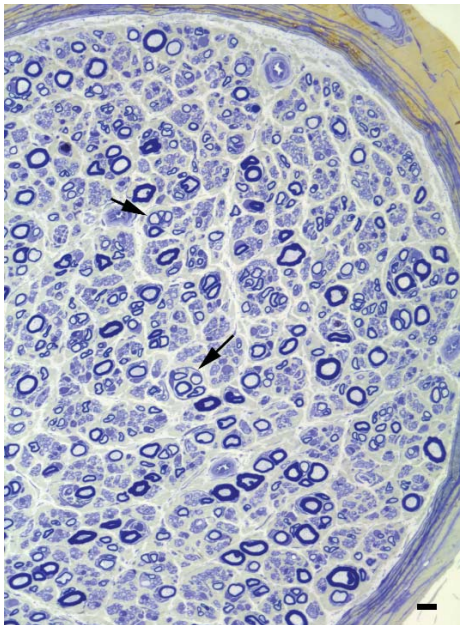

Figure 2: Nerve biopsy from a case of vasculitis showing numerous regenerative clusters (arrows). Bar = 10μm.

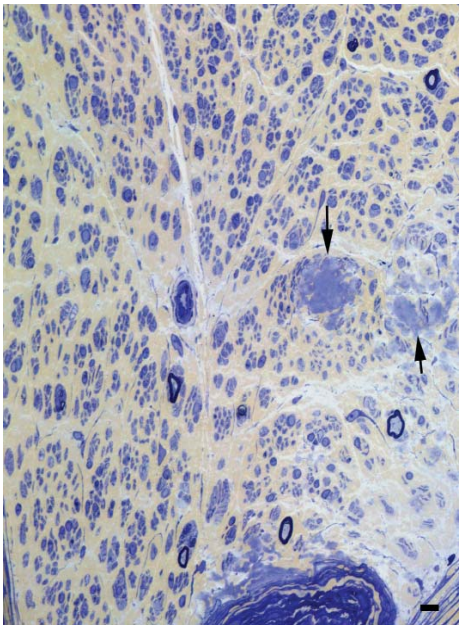

Figure 3: Nerve biopsy from a case of amyloid neuropathy. Arrows indicate amyloid deposits. There are very few surviving myelinated fibres. Bar = 10μm.

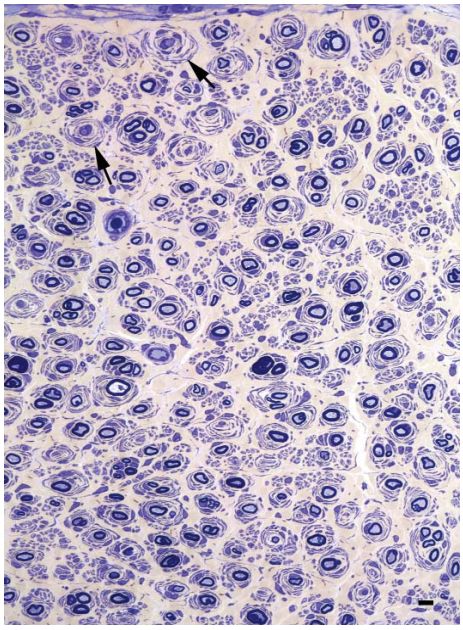

Figure 4: Nerve biopsy from a patient with hereditary motor and sensory neuropathy type 1a due to a duplication of the gene for PMP22. The are numerous 'onion bulbs' (myelinated fibres surrounded by circles of redundant Schwann cells). The central fibre occasionally lacks a myelin sheath (arrows) Bar = 10μm.

ina behind. In the normal nerve fibre, there is a correlation between myelin thickness and axon diameter but after remyelination the myelin sheath formed may be inappropriately thin for the axon calibre. Abnormal myelin composition may lead to instability and myelin breakdown and other diseases are due to a failure of the Schwann cell to maintain its myelin sheath although the myelin itself may be normal. Axons may also be damaged as a secondary reaction to myelin damage by a process not yet understood.

Axonal (Wallerian) degeneration on the other hand primarily damages the axon. Without axonal structure to support the myelin sheath, it collapses to form myelin ovoids. Initially these may be relatively long and contain some axonal debris but they breakdown further into smaller myelin figures and eventually to neutral fats and lipids. Teased fibre studies show strings of myelin debris along the length of the fibre distal to the site of breakdown. Axonal regeneration is possible depending on the cause, extent and site of the original damage. It is accompanied by extensive Schwann cell multiplication but these are not restricted to the region around the original fibre. Each regenerating axon can produce several smaller axons sprouts, some of which may remain too small to myelinate. This results in regenerative clusters that are the hall mark of axonal regeneration. The absence of these in a biopsy may indicate neuronal death. Regenerating axons may have inappropriately thin myelin sheaths and if they are not part of a regenerating cluster can be confused with remyelinating fibres. Studies on nerve fibres teased out individually are invaluable for distinguishing regeneration from remyelination. Regeneration leads to a series of short internodes all of the same length and myelin thickness whereas remyelination results in a variation of both myelin thickness and internodal length. Pathological alteration of the axonal diameter can lead to secondary demyelination.

Clinical features of neuropathy

Damage or loss of function of somatic nerves results in altered sensation (numbness or paraesthesiae) if a sensory nerve is affected or weakness if a motor nerve is damaged. Diseases affecting predominantly small nerve fibres result in altered pain and temperature sensations with relative preservation of muscle strength, tendon reflexes, touch-pressure, vibration and joint position; autonomic nerves may also be affected. Neuropathies affecting mainly larger fibres, on the other hand, show the reverse with loss of tendon reflexes, touch, pressure and joint position sensibilities and weakness due to lower motor neuron involvement. Neuropathies may be focal or multifocal (locally affecting only one or more peripheral nerve trunks) or polyneuropathy with widespread and symmetrical involvement of many nerves. Symptoms may be negative (for example, numbness or weakness) or positive (for example, tingling or muscle fasciculations).

Clues as to the cause of the neuropathy may be obtained by careful investigation of the distribution of the abnormalities, careful questioning about possible family history, blood and urine tests, chest x-ray, nerve conduction and CSF studies.

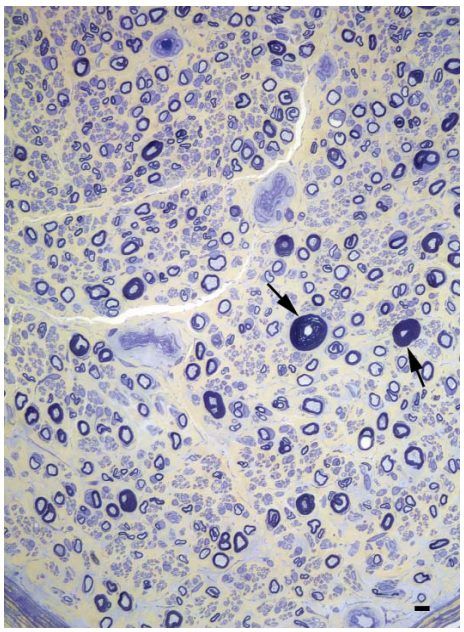

Figure 5: Nerve biopsy from a case of HNPP due to a deletion of the part of chromosome 17 coding for PMP22. Arrows indicate abnormally thickly myelinated tomacula. Many fibres have abnormally thin myelin. Bar = 10μm.

Indications for nerve biopsy

Nerve biopsy is an invasive procedure so other routes to diagnosis are carefully explored before deciding on removing a sample of nerve. The most frequent indication is probably an asymmetrical neuropathy affecting for example, nerves in one leg or arm and not the other. The most common cause of such findings is vasculitis but hereditary neuropathy with liability to pressure palsies (HNPP) (see below) may also present with a similar distribution. Vasculitis may affect only small blood vessels or only larger ones and may be restricted to the peripheral nervous system and not affect any other tissue. Distinguishing between tissue specific vasculitis and chronic inflammatory demyelinating polyneuropathy (CIDP) is a frequent indication for nerve biopsy and both disorders are potentially treatable. A patient may also have several possible causes of neuropathy so a biopsy may be done to distinguish between these.

How a nerve biopsy is done

The most frequently biopsied nerve is the sural nerve in the ankle. This is a small sensory nerve that can be removed without causing any long-term problems for the patient. Over the years this nerve has been so well studied that its normal and diseased structure are well understood. It is relatively easily accessible. The choice of nerve depends on the distribution of symptoms and

Table 2. Diagnostic abnormalities:

DISEASE	PATHOLOGY
Inflammatory neuropathies	Cellular infiltration
Vasculitis	Blood vessel necrosis
Paraproteinaemic neuropathies	Widely spaced myelin (EM)
Lipid storage diseases	EM of specific Schwann cell inclusion
Peripheral lymphomatosis	Immunocytochemistry
Solvent abuse	Patchy giant axonal changes
Hereditary neuropathies	Classical onion bulbs (HMSN1) Giant axonal changes (GAN)
Amyloidosis	Extracellular amyloid deposits
Leprosy	Bacterial infiltration

the results of nerve conduction tests. Where symptoms primarily involve the upper limbs the superficial radial nerve or other nerve in the arm may be sampled instead.

The biopsy is carried out by making a small incision in the skin , finding and then freeing the nerve and then gently cutting out a segment and removing it.[1] Nerves are very fragile so this procedure must be done with great care.

What happens to the nerve after biopsy?

The specimen is put on a piece of card to keep it straight and then carefully cut into several pieces. Unlike many other tissues, a routine haematoxylin and eosin stain on paraffin blocks yields relatively little information; this is only suitable to investigate inflammatory infiltration. The processing involved dissolves most of the myelin that is an important component of the nerve. The nerve specimen should be divided into 3 pieces; one for immediate freezing in liquid nitrogen, a piece for fixation in glutaraldehyde and another piece for formalin fixation. The frozen specimen in used for techniques that cannot be performed on fixed tissue and to give a quicker result for others. The glutaraldehyde fixed piece, when processed and embedded in epoxy resin, gives the best possible morphological preservation but does not allow for any biochemistry or immunohistochemistry.

How to diagnose a neuropathy from histology[2]

The frozen piece of nerve allows very rapid assessment of inflammatory cells; frozen or paraffin sections are used for immunostaining to identify them. The resin embedded pieces allow identification of changes to the myelin sheath and the axon with much greater confidence than can be obtained with a paraffin embedded section; lipid inclusion are preserved whereas they would be dissolved by paraffin processing. The sections are much thinner allowing greater resolution of the structure and ultrathin sections for electron microscopy can be cut from the same block.

It is vital to have some clinical details about the patient's history; what may be of little significance in old age may be highly important in a young person; eg. widening of the basal lamina round endoneurial blood vessels is frequently seen and uninformative in an elderly patient but is often found in diabetic neuropathy in younger people. If morphometric investigations are planned it is necessary to have age matched controls; the adult myelinated fibre size distribution is not attained until about 12 years of age.[3]

The type and distribution of inflammatory cell infiltration can be very helpful in diagnosis. T lymphocytes may indicate chronic inflammatory demyelinating polyneuropathy (CIDP) but may also be found in tissue specific vasculitis (affecting the Peripheral Nervous System only). In the latter case the presence of inflammatory cells within the vessel wall should be carefully sought. Necrotizing vasculitis is diagnostic when found but is very patchy and is difficult to identify in small venules. Numerous regenerative clusters in the same stage of recovery (Figure 2) are most likely to result from repair after vasculitic damage to all the axons simultaneously. Active demyelination with myelin stripping seen by electron microscopy, on the other hand, indicates an autoimmune attack on the myelin (Guillain-Barré syndrome (GBS) or CIDP) but this may affect very few fibres at any particular time and may easily be missed. Occasional demyelinated fibres may be found in elderly people without a clinical neuropathy. The main pathological changes associated with specific neuropathies are listed in Table 2; other helpful features are listed in Table 3.

Deposition of amyloid protein in clumps between the nerve fibres is found in primary and secondary amyloidosis (Figure 3). Amyloid is a fibrillar protein identifiable by electron microscopy and by special stains by light microscopy.

Table 3. Helpful pathological findings:

DISEASE	PATHOLOGY
CIDP	T-cell infiltration Demyelination
Diabetic neuropathy	large, round regenerative clusters, excess basal lamina around blood vessels, persistent Schwann cell basal lamina after degeneration (EM)
Paraproteinaemic neuropathies	Demyelination Excess basal laminae around endoneurial blood vessels
Small fibre neuropathies	Morphometric demonstration of small myelinated fibre loss
Hereditary neuropathies	Onion bulbs (HMSN1), Tomacula (HNPP), Basal laminal onion bulbs (many =PMP22 point mutation, few =KIAA1985 mutation)
Systemic vasculitis	Inflammatory infiltration of vessel walls Axonal loss/regenerative clusters

Quantification of the nerve fibres may be helpful in diagnosis as some neuropathies affect one specific fibre type.[4]

Hereditary neuropathies

The most frequently encountered are the hereditary motor and sensory neuropathies (HMSN) also called Charcot Marie Tooth Disease (CMT). There are numerous genetic mutations causing either CMT1 (demyelinating) or CMT2 (axonal) and more are being published every day. Peripheral myelin protein molecular weight 22KDa (PMP22) comprises only about 10% of the protein in the myelin sheath but it is implicated in the majority of hereditary demyelinating diseases. The commonest, CMT1A, is due to a duplication of the gene region including PMP22. Finding numerous onion bulbs even without a family history suggests PMP22 duplication but this can give rise to very variable clinical phenotype and pathology ranging from recent focal demyelination to the presence of numerous classical onion bulbs (Figure 4). Finding inflammatory infiltrates does not preclude an hereditary neuropathy.[5] Some relatively common genetic neuropathies can be easily missed. In particular, hereditary liability to pressure palsies due to a deletion of the part of the gene encoding for PMP22 usually manifests as an asymmetrical neuropathy with spontaneous resolution but the clinical signs and symptoms are very variable and there is often no family history. The typical pathological change is thickening and/or abnormal folding of the myelin sheath in localised regions to form tomacula. (Figure 5) These may be more easily identified in teased nerve preparations. They may also be found in CIDP and in neuropathies associated with IgM paraproteinaemia but their presence in a biopsy should be sufficient to send a DNA sample for analysis of the PMP 22 gene. It is becoming clear that many undiagnosed and undiagnosable neuropathies are in fact genetic in origin. It is to be hoped that biopsies will be taken from patients with genetic mutations so that this situation can be remedied and the pathological changes found can lead to an identification of the genetic mutation. There is a website devoted to hereditary neuropathies which is kept up to date and lists all the mutations so far identified.[6]

A new edition of 'Peripheral Neuropathy' covers the peripheral nervous system in extensive detail.[7]

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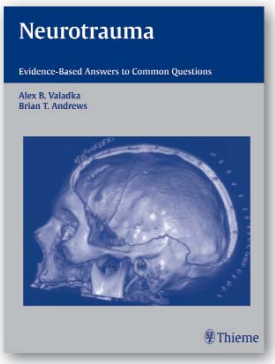
Neurotrauma - Evidence-Based Answers to Common Questions



Alex B Valadka, Brian T Andrews
Published by:
Thieme Medical Publishers
ISBN: 1588902668
Price: €89.95

There is a paucity of randomised controlled trial evidence covering neurotrauma topics. However, this book provides an excellent review of the available literature and addresses many clinical controversies.

Neurotrauma is a multi-author text, mainly of North American origin. It comprises 48 chapters covering seven domains of care. Each chapter is prefaced by a management-based question, directed at relevant clinical situations. These cover immediate care through acute hospitalization to after care. Although such an approach is not universal it does provide focused well-researched accounts.

A recognised expert author scribes each chapter. The chapters are designed to review the literature for each topic from an evidence-based perspective. Where appropriate, evidence and recommendations are categorised into levels I – III. A personalised view, based upon experience in the subject area is also valuable. The highlighting of 'pearls of wisdom' provides an accessible synopsis of each subsection.

Many of the chapters are of extremely high quality and merit a wide readership. A well-informed account of the use of head injury assessment scales is worthy of attention. The use of intensive care monitoring, such as jugular venous oxygen saturation and brain tissue PO2 in the modern setting are reviewed. Outstanding contributions covering the use of mannitol therapy, the diagnosis and management of hyponatraemia and hypothermia are included. Finally, a balanced view on the management of spinal cord injury is presented.

As is expected in a book of this nature, some useful references are omitted, presumably due to the lengthy process of writing, editing and publishing.

Overall, I strongly recommend this book to Accident & Emergency doctors, neurosurgeons and intensivists. Many paramedical therapists may also find the content useful and accessible.

Peter C Whitfield,
Consultant Neurosurgeon and Honorary University Fellow, South West Neurosurgery Centre, Plymouth, UK.

Neurology - 2nd Edition

Michael Donaghy
Published by:
Oxford University Press
ISBN: 0-19-852636-9
Price: £21.99

In this book the author aims to provide a sound clinical approach to the common problems encountered in neurological practice, and to teach pertinent neurological examination. Let's face it, neurology is a tricky subject to get your head round, especially when just beginning. Often texts in neurology try to tempt medical students by shortening and trying to make the subject 'snappy'. Unfortunately this difficult subject does need some time spent on it, and the time spent reading this book will be well rewarded.

The book is divided into chapters, the first couple being dedicated to basic neurological history and examination skills. The concept of 'weakness' is then tackled in a systematic way including that due to brain and spinal cord, nerve root, peripheral nerve and lastly muscle. Further chapters are based on more specific neurological problems such as facial pain, speech, and disorders of gait. Some subjects appear to have been given slightly more coverage than others. For instance, peripheral neuropathies are discussed in far greater depth than other subjects such as seizures or issues to do with enablement. This may indicate the author's subject of interest, but may not entirely reflect the needs of the average medical student.

Excellent clinical and radiological illustrations are used throughout. Case histories are used well, either to demonstrate 'real life' situations related to diagnoses in the chapter, or to discuss important differential diagnoses. The case histories keep the reader interested and are very sensitively written, the majority being of 'real-life' experiences encountered by the author.

The book explains which parts of the neurological examination are useful screening tests, and which are more suitable if examining for specific problems. Useful practical advice is given regarding technique and interpretation. We thought it was useful to have the four stations of the neurology examination made explicit: whilst the patient is telling their story, standing (and walking), sitting, and lying. The relevance and shortcomings of tests such as Romberg's test are considered, with the emphasis being on the useful information such tests offer the examiner. Such clinical advice is invaluable to this target audience.

We argued for some time about whether the illustrations on page 76 show how to test abductor pollicus longus or brevis and concluded that it was more longus than brevis! However this is a minor point and reflects how much we have used the book. Michael Donaghy's *Neurology* is a valuable introduction to clinical neurology for undergraduate medical students and we recommend it.

Dr Eleanor Pinnock, SpR in Neurology, Morriston Hospital, Swansea, UK &
Dr Tom Hughes, Consultant Neurologist, UHW, UK.

Optical Illusions

Optical illusions fascinate us, challenging our default notion that what we see is real. They demonstrate that all our perception is illusion, in a sense – incoming sensory information is interpreted, yielding the internal representation of the world. Therefore, after our eyes have filtered the visual input we need sound judgement of information in order to create our inner reality: "Your senses then you'll have to trust, / They'll let you see what's true and just, / Should reason keep your mind awake".[8]

What is an optical illusion? "I know it when I see one" could not be farther off the track – as the best illusions are the ones where a discrepancy from reality is not 'seen' until one uses other modalities (eg. touch) or instruments (rulers, light metres). And even when we know that we are subject to an optical illusion, most illusory percepts still persist – a phenomenon called cognitive impenetrability.[15] As Gregory[9] aptly stated it "it is surprisingly hard to define 'illusion' in a satisfactory way". According to the Merriam-Webster Online Collegiate Dictionary, an illusion is 1. something that deceives or misleads intellectually; 2. perception of something objectively existing in such a way as to cause misinterpretation of its actual nature.

Why study illusions?

Is it only the playful child in scientists that drives them to study optical illusions? To some degree, yes, but illusions can also decide major sport events: referee judgements probably are affected by the 'flash lag effect', eg. when judging the spot where a tennis ball touched the ground.[2] However, there are professional reasons as well: Optical illusions are particularly good adaptations of our visual system to standard viewing situations. These adaptations are 'hardwired' into our brains, and thus can cause inappropriate interpretations of the visual scene. Hence illusions can reveal mechanisms of perception.

There are also some clinical conditions in which optical illusions play a major role, eg. organic psychoses, epileptic aura and migraine. Another often overlooked[21] disorder is the Charles Bonnet syndrome:[4] patients with a normal cognitive status but reduced afferent sensory input due to visual system pathology (eg. age-related macular degeneration) or with brainstem pathology[6] experience visual hallucinations of various sorts. Finally, from a visual scientist's point of view the Rorschach test[17] is based on optical illusions or more precisely on the phenomenon that our brain is constantly looking for known patterns in random structures with low information content, called pareidolia.

What is old, what is new?

Some illusions are long known to mankind, eg. the waterfall illusion was mentioned by Aristotle: after staring at a waterfall for a couple of minutes neighbouring objects seem to be shifting upwards. This was followed up by Lucretius, Purkinje and Addams who coined the term 'waterfall illusion'. Recent evidence suggests that this motion aftereffect is not due to 'fatigue' but rather due to a gain adjustment, an optimal adaptation to prevailing conditions.[18] The description of numerous illusions, in particular geometric illusions, in the 19th century was followed by striking new ones, many of which rely on computer animation, in the last decade.

Classification

This abundance of illusions is hard to categorise, especially since many still lack a successful explanation. We will use the following six phenomenological groups:

- Luminance and contrast
- Motion
- Geometric or angle illusions
- 3D interpretation: size constancy and impossible figures
- Cognitive/Gestalt effects
- Colour

and show examples of the first four. Many more examples of illusions can be found at <http://www.michaelbach.de/ot>.

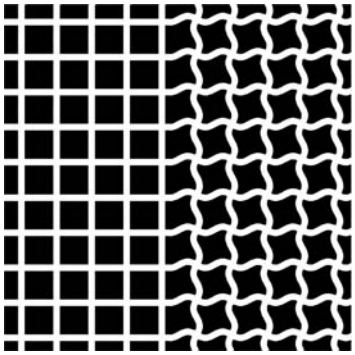


Figure 1: The Hermann grid on the left with grey patches at the intersections, and a new variant on the right[7] removing the illusionary patches.

Luminance & Contrast

The 'Hermann grid' was discovered in 1870 by the physiologist Ludimar Hermann.[11] If you examine the left part of Figure 1, you will notice faint grey patches at the intersections of the white 'streets'. These patches are not visible when directly fixated.

For half a century this illusion was explained on the basis of lateral inhibition;[3] this assumes that we see the world as our retinal ganglion cells encode and thereby compress it. However, in most situations our visual cortex undoes the retinal encoding by spatial integration to approach a veridical luminance perception. A complete explanation of the Hermann grid would have to include why this mechanism fails here. Recently János Geier showed that just a slight torsion of the grid lines abolishes the appearance of the grey patches (Figure 1, right part), highlighting the additional role of cortical processing, ie. orientation selective neurons.[7]

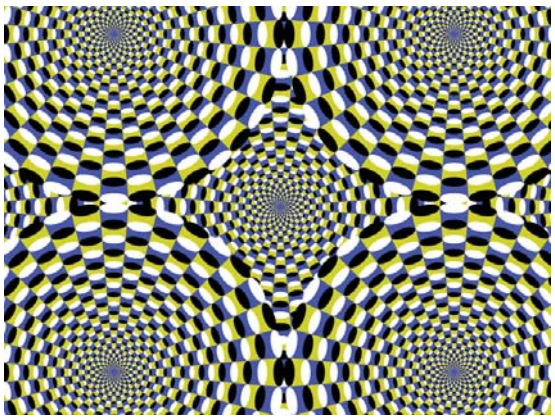


Figure 2: Kitaoka's 'Throwing cast nets'.

Motion

In Figure 2[12] the disks appear to expand slowly. It may take a few seconds and exploring eye movements to appreciate the effect – still, not everyone perceives this illusion.

The complete explanation of this illusion is not fully established in spite of promising recent efforts.[1,5,12] Prerequisites are: asymmetric luminance steps, eg. from dark to dark-grey and white to light-grey and eye movements. When they suddenly appear (= temporal modula-

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tion), the asymmetric luminance steps drive motion detectors.[10,16] The eye movements affect temporal modulation with the help of either adaptation[1] or possibly saccadic suppression. A grouping arrangement enhances the effect, but colour is not necessary.

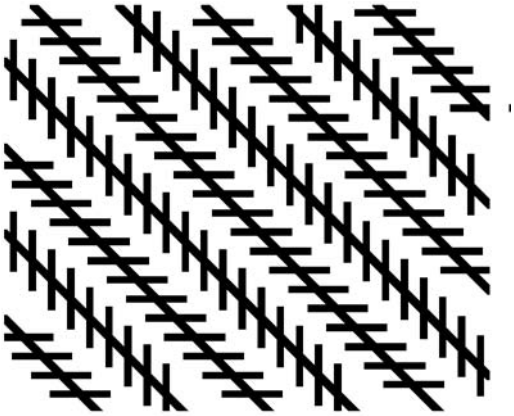

Figure 3: The Zöllner illusion. The oblique lines are all parallel.

Geometric or angle illusions

The German astrophysicist J Zöllner discovered in 1860 that parallel lines intersected by short lines at an acute angle appear to diverge (Figure 3): The crossings of the short lines evoke a depth perception so that one end of the long lines appears to be closer to the observer than the other. This class also comprises Fraser's Spiral, the Poggendorff and Hering illusions. Common to all of them is that small angles are overestimated, but the precise underlying mechanisms remain to be clarified.

Size Constancy

A large class of illusions is probably caused by size constancy. This is an important mechanism where our visual system multiplies retinal (or angular) size with assumed distance, enabling us to estimate size independent of geometrical perspective. Partially already present at birth,[20] we take size constancy for granted, only reminded of its ever-present action when it fails. The latter can happen when distance information is not available and our visual system resorts to 'default settings' – eg. in the moon illusion that lets the moon appear larger when it is near the horizon than when seen high in the sky – or when the 3-dimensional image interpretation is not appropriate – eg. the Ponzo illusion, or Shepard's 'Turning the Tables':[19]

If we had one table cloth, would it exactly cover both table tops in Figure 4, top? Certainly not. If we were to cut out one table top from the paper, would it cover the other one? Indeed yes, they are identical parallelograms, as shown in the bottom of Figure 4. This example demonstrates that one cannot deduce from optical illusions that our eyes 'deceive' us. Both answers above are correct. The observer's irritation stems from our automatic interpretation of line drawings as renderings of 3-dimensional objects, a very good strategy for most of our life. This automatic 3D interpretation is so strong that it is hard, if possible at all, to envisage the table tops as flat parallelograms.

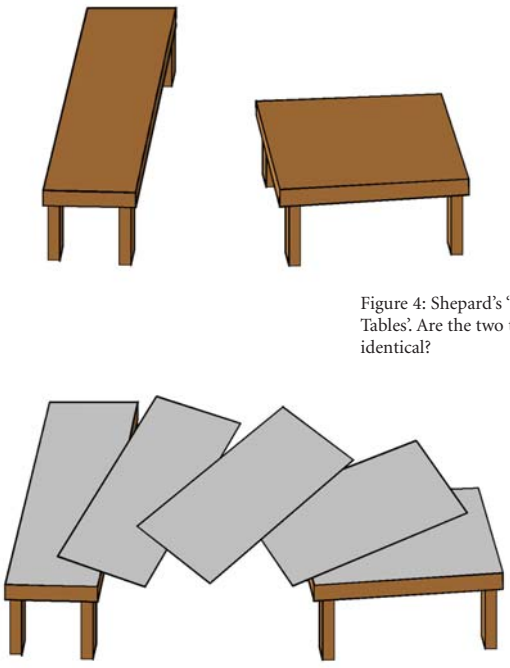

Figure 4: Shepard's 'Turning the Tables'. Are the two table tops identical?

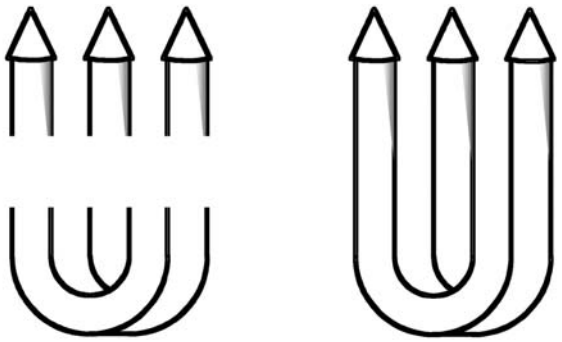

Figure 5: The impossible trident, also known as blivet or devil's fork.

Impossible Figures

Consider Figure 5 (left) above. The upper part is easily conceived as three towers, the bottom catches our eyes as a rod bent into a U-shape. Both interpretations are perfectly valid. If, however, the lines are connected as seen in the right part, an 'impossible object' emerges. The line continuations are not appropriate, because they turn the empty background between the towers into surfaces of the U at the bottom. The observer is left with an uncanny percept, and both art and science are linked here: Mauritius Escher drew his "Ascending and Descending" only two years after Penrose[13] published the 'impossible staircase' drawing.

Future

Plato[14] already alerted us to the discrepancy between perception and reality in his "Allegory of the Cave". In all likelihood we will never be able to turn around and see the true reality, but we can do our best to understand it. Many illusions remain unsolved to date, and there will be more to come. In the meantime, we can enjoy their viability as a research tool, and also to introduce the next generation to the fascination of science.

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Rehabilitation Following Traumatic Brain Injury: Challenges and Opportunities

Background

The principles underlying the rehabilitation needs for patients with head injury have been recognised since the Second World War.[1] Since that time, numerous official reports have highlighted major deficiencies in service provision and make similar recommendations for an integrated service. However, recent national reports[2,3,4,5] and a comprehensive survey in the Eastern Region[6] have still found that whilst there are models of excellence, core service provision in the UK remains variable, inequitable and under-resourced. This is acknowledged and supported nationally by those with expertise in, and understanding of, the needs of brain injury survivors, their families and carers from across the spectrum of health and social services, and voluntary agencies.

Traumatic brain injury is the leading cause of disability in people under 40 years of age, and severely disables 150-200 people per million annually. It is now estimated that 200 - 300 per 100,000 of the population have a significant disability as a result of head injury. Survival rates following severe brain injury have improved dramatically in recent years due to advances in acute care, potentially increasing the requirement for rehabilitation.[7,8,9] The majority of head injuries, however, are designated as minor and moderate and after initial management there is little or no follow up and support, yet recent studies show that a significant proportion of these may suffer persisting symptoms after what appears to be a minor injury. [10] The need for comprehensive and effective rehabilitation programmes for these individuals is therefore ever increasing. Moreover, these patients can suffer considerably and there can be a significant economic impact in terms of delayed return to work and normal activities.

Rehabilitation medicine is a relatively new specialty, having been recognised as a separate discipline only in the past 20 years, and as yet there are relatively few trained rehabilitation specialists. Although it has traditionally been a low profile medical speciality, attitudes are changing and the importance of early rehabilitation intervention to optimise the long term outcomes of head injury is now increasingly recognised. There have been a number of recommendations for neurorehabilitation, and the process of developing guidelines is ongoing, the most recent being the national guidelines for rehabilitation following acquired brain injury which seek to address the complex and three-dimensional nature of rehabilitation.[11]

This review describes some of the challenges presented in planning and delivering effective rehabilitation services to head-injured patients and explores solutions and opportunities in the light of current development of the National Service Framework for Long-term Neurological Disabilities, which sets a national framework to enable local development, implementation and commissioning of services.[12]

Challenges

A number of challenging issues have been identified, defined and explored by the Eastern Head Injury Study in relation to neurorehabilitation, in particular the assessment of the organisation and clinical management of head injury in the Eastern Region. These are, however, common to neurorehabilitation services throughout the UK. Over time, a variety of rehabilitation models have developed across the NHS.

1. Complex needs of head-injured patients

Head-injured patients have complex and varied needs; the nature of disability following head injury is diverse resulting in a complex interplay of problems that can be physical, cognitive, behavioural, vocational or a combination of these, requiring multi-organisational involvement in the provision of rehabilitation. Consequently many specialties, professions and sectors may be involved in the process of rehabilitation, resulting in a lack of, or disjointed, untimely or inappropriate rehabilitation care and ongoing support for many patients. This has led to difficulties in co-ordination and integration of service provision (Figure 1).

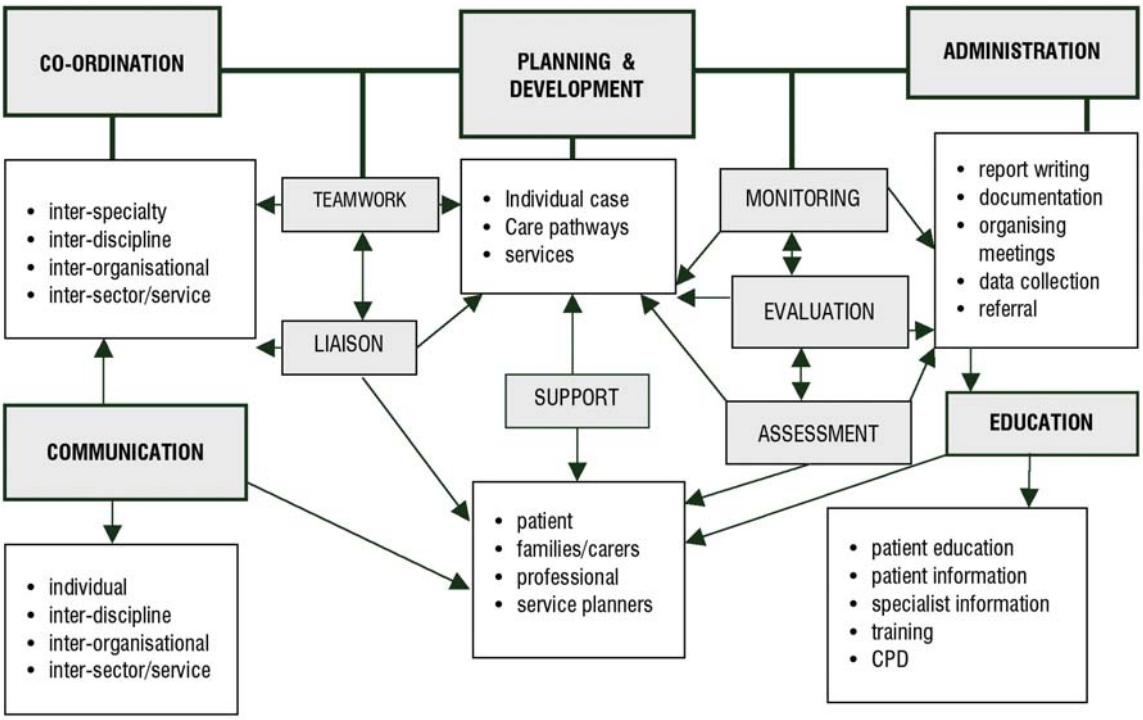

Figure 1: Multiple core skill requirements for co-ordination of Head Injury Services.

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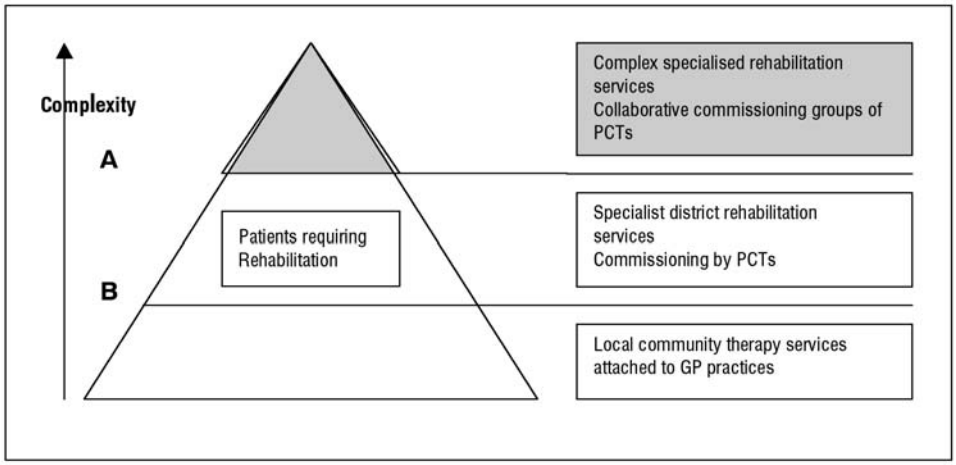

Figure 2: The different levels of rehabilitation service provision (the top tier above A denotes specialised service)
From: DOH Specialised Services National Definitions Set (2nd ed.)

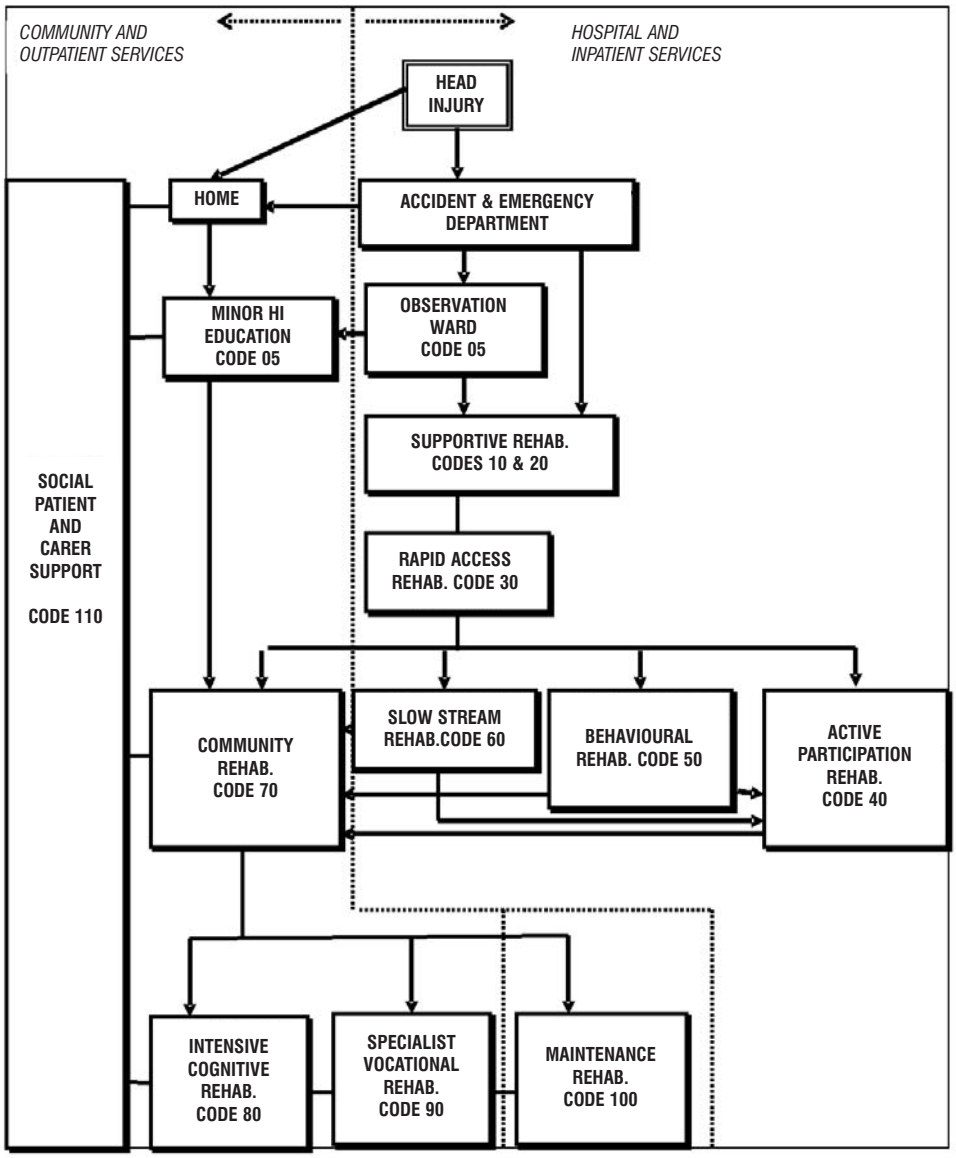

Figure 3: Flowchart of potential head injury rehabilitation services using the EHIG Rehabilitation Codes.

Divisions of service and the ensuing variety in responsibility of care have led to fragmentation of services and poor co-ordination. In addition, there are difficulties within statutory services relating to categorisation of head injury which have resulted in lack of knowledge of the nature and extent of the problems and poorly defined care pathways for mild/minor, moderate and severe head injuries.

2. Poor resources

In the Eastern Region, the Eastern Head Injury Resource Study found that no area has easy access to the whole range of services that would constitute a truly comprehensive neurorehabilitation service.[6] The picture is similar throughout the UK.

While the need for early rehabilitation in an appropriate setting and adequate follow-up is recognised, the variability of facilities and resources often result in 'bottlenecks' with delayed and inappropriate referrals. Lack of adequate and appropriate rehabilitation facilities at all stages of rehabilitation can lead to blocked beds in District General Hospitals and inappropriately placed patients (acute admissions of moderate head injuries and repatriation of severe head injuries). Delays in transfer and discharge to each stage of rehabilitation may also be detrimental to the outcome of the head-injured patient. Another effect of blocked beds is the potential delay in elective surgery.[13] Other resource deficiencies are lack of staff trained in the management of head injury and a national lack of neuropsychologists.

3. Commissioning issues

Bureaucratic and funding barriers may also prevent timely access to appropriate services. Long-term conditions like head injury make care particularly complex, and a small number of patients and diseases account for a disproportionate amount of healthcare use, both inpatient and community, making them high risk/low volume services (Figure 2).

Responses to rehabilitation need to coincide with increased awareness of economic efficiency of health care provision.[14] This must be balanced with need and demand, equitability, efficiency and effectiveness. There are major cost implications in a comprehensive rehabilitation service for head injured patients. However, this should be balanced against the fact that effective rehabilitation may reduce dependence on carers and services over time, and implications for reducing the cost of overall care and impact on the health of carers. Measurable change and recovery may continue for several years post injury, so that rehabilitation services may be required for some considerable time for recovery to be maximised.

There is currently a lack of integration in commissioning services and many of the organisational problems in developing these services arise from this process. There are different levels of commissioning and different agencies are involved in the planning and development of services that require an integrated approach. Matching the level of care to the level of need calls for whole systems approaches to whole populations. The focus must be on service users as the pattern of the rehabilitation stages and process are dictated by the nature of disability. This poses a problem for commissioning head injury rehabilitation as social services commission independently from health.

4. Lack of evidence/research

The importance of evidence in support of demand, need and the effectiveness of rehabilitation for the head injured is emphasised as being particularly relevant with the increasing

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in scar formation. Debridement or skin grafting required occasionally. With multiple lesions, stop therapy until healing occurs. With single lesions therapy may be continued. Advise patients to use an aseptic injection technique and rotate injection sites. Periodically review patients' self-injection procedures. *Drug interactions:* 28 days of corticosteroid or ACTH treatment has been well tolerated. Use of other immunomodulators is not recommended. A down regulation of hepatic cytochrome P450 has been reported with interferons. Exercise caution when administering with drugs that have a narrow therapeutic index and are dependent on the hepatic cytochrome P450 system for clearance. Caution with any drugs affecting the haematopoetic system. **Side effects:** The following adverse events collected as spontaneous reports are classified as : very common ≥ 10%, common <10% - ≥1% , uncommon < 1% - ≥0.1% , rare <0.1% - ≥ 0.01%, very rare < 0.01%. *Very common:* flu-like symptom complex, chills, fever, injection site reaction, inflammation, injection site pain. *Common:* necrosis. *Uncommon:* anaemia, thrombocytopenia, leucopenia, increase in ALT, AST, hypertonia, depression, hypertension, nausea, vomiting, alopecia, urticaria, pruritus, rash, myalgia. *Rare*: lymphadenopathy, thyroid dysfunction, γ-GT and triglyceride increase, convulsion, confusion, anxiety, emotional lability, cardiomyopathy, tachycardia, palpitation, bronchospasm, dyspnoea, pancreatitis, hepatitis, skin discoloration, sweating, menstrual disorder, suicide attempt, anaphylactic reactions, malaise, chest pain. *Very rare:* hypocalcaemia, hypercalcaemia, depersonalisation. Other adverse events reported during clinical trials are: lymphopenia, neutropenia, altered laboratory tests for glucose and urinary proteins, peripheral oedema, dizziness, insomnia, conjunctivitis, ear pain, migraine, vasodilatation, sinusitis, increased cough, diarrhoea, constipation, skin disorder, myasthenia, urinary disorders, impotence, pain in various sites, asthenia, infection, abscess. The incidence rate of injection site reactions decreases over time. If breaks in the skin occur advise patients to contact their physician before continuing with injections. For further information please refer to the SmPC. **Legal category:** POM **Basic NHS price:** £596.63 for 15 x 3ml Betaferon vials with diluent. **PL numbers:** EU/1/95/003/001, EU/1/95/003/002 **PL holder:** Schering Akteingessellschaft, D-13353 Berlin, Germany. **Date of preparation:** 24 January / 03.
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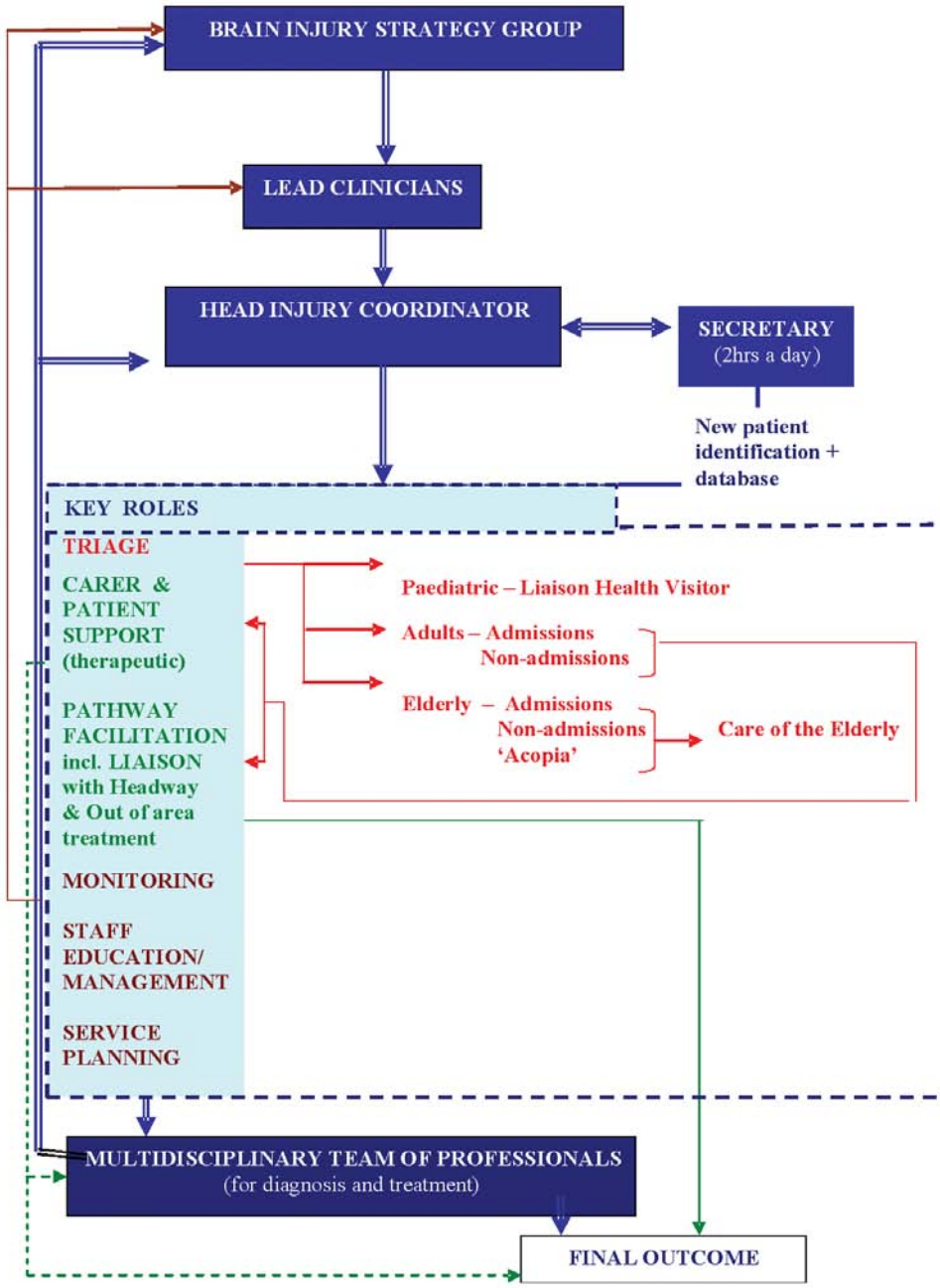

Figure 4: Template for co-ordination of Head Injury Services.

need to justify the use of limited resources within the NHS. However, the treatment of neurological disability is a major challenge for translational research. Complex interactions between the individual and their environment make accurate and reliable outcome measurement difficult. Rehabilitation aims to reduce the impact of head injury by restoration of damaged function or compensation for lost function within the limitations of resources and underlying disease to optimise physical, cognitive, psychological and social function. Measurement of the impact of rehabilitation is therefore difficult. Rehabilitation is a patient-based educational process towards optimum quality of life, yet clinically orientated outcome scales of disability and impairment are most often used and therefore only partially reflect the rehabilitation process.

The greatest burden is from the neuropsychiatric sequelae. However, the emphasis has been on physical rather than cognitive needs in early assessment post injury. This may explain why unmet need is most evidenced in cognitive and psychological rehabilitation.[15]

Opportunities

While the challenges in providing quality neurorehabilitation services are many, the experiences of the Eastern Head Injury Group have shown that with a whole systems, collaborative and stepped approach, systematically working with and integrating new evidence and initiatives and improving co-ordination, there are opportunities for achievable, affordable solutions.

1. Standards, templates and codes

As a result of addressing key issues of variability and gaps in the provision of rehabilitation of head injury, the Eastern Head Injury Group has developed a service framework from initial injury to reintegration into the community, together with a set of planning and evaluation tools collaboratively developed through an iterative process. These consist of a set of Head Injury standards for Acute Hospitals, which complement the Society of British Neurological Surgeons, the National Institute for Health and Clinical Excellence and the National Service Framework,[16] a set of Rehabilitation Definitions which clearly define and map the stages of the rehabilitation care pathway,[17] (Figure 3 and Table 1) and a Head Injury Co-ordination Template (Figure 4), which details the various roles necessary for good service co-ordination, defining responsibilities and an accountability structure. Using these codes has identified a complete lack of rapid access rehabilitation (Code 30) in the Eastern Region.

These practical tools are designed to assist service planners and providers to develop and maintain optimum quality and responsive rehabilitation services and contribute to the growing evidence-base confirming the efficacy of a holistic and interdisciplinary approach to rehabilitation after TBI at the same time enabling services to be tailored to local needs and resources, complementing the evaluation of planning and thinking of the National Service Framework on long-term disabling conditions.

2. Resources

Resources will always be an issue, but the EHIG found that there are elements of services in most areas that could provide the basis for further development. Also mapping of current resources and the use of the rehabilitation codes and co-ordination template can identify gaps and variability to form the basis of business plans and care pathways.

Again, the whole systems and collaborative approach of the EHIG found that reallocation of resources can also be a solution, using the head injury co-ordination template. The development of networks and head injury coordinator-type posts assist co-ordination, develop communication systems and patient care pathways, by working across care settings and professions.

Conclusions

The management of the growing numbers of people with long-term conditions remains problematic. Developing a co-ordinated, personalised service across acute and community settings presents immense organisational and cultural challenges to the whole health and social care spectrum.

The National Service Framework for long-term conditions in the UK[12] describes how timely access to services can be achieved. The Quality Requirements (QRs) are particularly relevant to TBI and rehabilitation and set standards for specialised rehabilitation with markers of good, evidence-based practice. It provides guidance on establishing Neuroscience Networks to co-ordinate a collaborative, multi-agency approach to commissioning equitable services throughout the care pathway. Existing network models such as cancer, cardiac and renal, are good examples. The collaborative working required by networks and the now necessary multidisciplinary approach to the provision of head injury rehabilitation has the potential to facilitate implementation of complex changes and strengthen service co-ordination. This would be achieved

Table 1: Classification of head injury recovery and actual/ potential rehabilitation services for adults in the Eastern Region

Code	Title	Patient description	Sites	Examples	Description of rehabilitation input
05	Minor HI education	Medically stable, requiring 24-48hrs observation prior to community rehabilitation, (as necessary in a small minority) with low probability of acute neurological deterioration requiring neurosurgical advice/transfer	Acute A&E observation ward	Addenbrooke's, Peterborough Bedford	Assessment and observation - education, emotional and social support. Planned discharge home or moves to code 30 at 48 hours
10	Supportive rehab	Medically unstable, requiring neurosurgical or critical care	Acute hospital	Neurosurgical unit	Identifying and addressing early rehab goals before medically stable and transfer of care to rehab team
20	Supportive rehab	Medically unstable, not requiring neurosurgical or critical care	Acute hospital	Acute hospital ward	ditto 10
30	Rapid access rehab	Medically stable, not (necessarily) able to actively participate due to, post traumatic amnesia (PTA), confusion, rejection, low response or awareness.	Acute hospital	National Hospital for, Neurology and Neurosurgery, London, Brain injury services (Current practice: DGH - GSUR, ORTH,NLGY)	Needs inpatient care due to physical dependency & requires continuous clinical assessment (nursing, medical, therapy) in order to facilitate optimal timing for rehab input and detect deterioration in clinical condition (in minority of patients). Immediate early rehab delivered, and judgement made on timing/appropriateness of referral to next rehab sector.
40	Active participation in-patient rehab	Medically stable, able to actively participate with and benefit from therapy.	Acute or community hospital	In-patient rehabilitation unit (Lewin / Colman)	Needs in-patient care due to physical dependency, or need for specialist therapy equipment, safe environment, supervision or intensity of therapy which can not be provided in community
50	Behavioural rehab	Medically stable, but prolonged confusion or behavioural difficulties, amnesia requiring specialist behavioural management, intensive supervision and secure environment	Specialist in-patient unit	Brain Injury Services, Kelmsley Unit, Northampton BI Rehabilitation Trust, M.Keynes, Colman	Specialist behavioural management, including high staffing:patient ratio to ensure intensive supervision and secure environment. Access to neuropsychology and neuropsychiatry
60	Slow stream rehab	Medically stable, but low awareness or response persists beyond eg. 3 weeks after sedation withdrawn and ICP corrected. Able to benefit from medical and physical therapy to prevent complications and support recovery.	Community hospital or specialist in-patient unit	Putney, Wayland, Lincoln	Assessment/active rehabilitation phase which needs to be distinguished from long term care, although planning care increasingly important aim after some (eg. 6) months. Patients may go to active participation unit if they improve sufficiently.
70	Community rehab	Medically stable, able to actively participate with and benefit from therapy. Will include spectrum of initial severity of injury with a small minority derived from Code 05 category	Domiciliary or day hospital	Community rehab team (Icanho, Pboro)	Interdisciplinary co-ordinated management therapy aimed at community re-integration /inclusion by enhancing independence, wellbeing, & assist return to work/education. In collaboration with Social Services, voluntary and statutory services. Includes treatment of patients in residential care or with live-in carers
80	Intensive cognitive rehab	Medically stable, independently mobile, primarily cognitive impairments likely to benefit from intensive neuropsychological therapy	Domiciliary or day hospital	Oliver Zangwill	Aiming to return to work, studies or independent community life.
90	Specialist vocational rehab	Medically stable, living in community, aiming to enter/return to employment	Domiciliary or residential	Papworth Rehabilitation, Rehab UK	Aiming for return to work where this is influenced by physical or cognitive problems or needs residential placement
100	Maintenance	Medically stable, but permanent disability	Domiciliary, residential or nursing home, respite unit	Community therapists, Sue Ryder	Prevent deterioration of physical, emotional and behavioural condition, and long term management of seating, pressure, spasticity etc.
110	Social, patient and carer support	Carer support from initial injury, patient support when able to communicate	All sites	Headway	Developing social skills, stamina, confidence, attention & leisure pursuits, sorting out benefits, day supervision & respite care. Specific attention paid to: Community involvement & integration (further education etc) Personal social development and empowerment Structured daytime activity with the individual's competency framework Information and guidance over a continuum Family support and outreach; Advocacy

by identifying and strengthening existing communication systems, and improving information systems such as the development of clear patient care pathways across care settings and professions.

Recent advances in neuroscience treatments and rehabilitation research has also made considerable strides in the last two decades in developing robust measures at different levels due to advances in neuroscience. The advent of a range of brain imaging techniques such as MRI and PET scanning and advances in cognitive neuroscience have enabled greater understanding of brain damage and neurological recovery. This is revolutionising the measurement of outcome in neurological patients, and new multi-dimensional measurement tools are being collaboratively developed.[18] Also, the research and audit programme carried out in the Eastern Region over the past 12 years demonstrates that the problems of transforming a complex service are not intractable or necessarily costly and the service planning tools developed give opportunities for significant improvements across the UK. Whether the NSF and other strategies provide the necessary resource to deliver these opportunities remains to be seen.

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The Circadian Clock and its Genes: in the Brain and Beyond

The holy grail of molecular neuroscience is to explain how the activity of specific suites of genes within defined neuronal populations leads to adaptive behaviour. Recent analyses of the molecular genetic and neural bases of circadian timing provide a cardinal example of such genes-to-cells-to-behaviour reductionism. In doing so, the lid has been lifted on a neuroscientific 'black box' to reveal a cellular timing mechanism that has a pervasive impact on most tissues of the body and, hence, on mental and physical well-being.

Circadian rhythms are those daily cycles of physiology and behaviour driven by an internal 'body' clock. They therefore continue to 'free-run' with a period of approximately (circa-) one day (dies) when an individual is experimentally isolated without time cues. Our most obvious circadian rhythm is the cycle of sleep and wakefulness, but this is complemented by a multitude of physiological rhythms many of which (epithelial cell division, hepatic detoxification and systolic blood pressure) have direct clinical relevance. In nature, these internal programmes are synchronised to each other and to the 24 hour solar cycle, enabling our physiology to adapt to the challenges and opportunities presented alternately by day and by night. In modern life, however, changing socio-economic demands, increased longevity and associated neurodegenerative disease disrupt this fine-tuning.[1] For example, shift workers experience increased incidence of metabolic diseases,[2,3] whilst sleep disturbance is an extensive problem for the elderly[4] and the principal cause of institutionalisation in Alzheimer's disease and related disorders[5] (Figure 1).

The suprachiasmatic clock

The circadian pacemaker of the brain is the suprachiasmatic nuclei of the hypothalamus (SCN) (Figure 2a). When isolated in vitro these bilateral clusters of ca. 10,000 neurons continue to exhibit circadian cycles of metabolism, electrical firing, neuropeptide secretion and gene expression.[6] Circadian time is not, however, an emergent property of a neural network. Many if not all SCN cells are autonomous clocks: a remarkable localisation of neural function. The ventral core of the SCN, characterised by GABA-ergic cells that co-express vasoactive intestinal polypeptide (VIP), receives afferents principally from the retina and brain stem that synchronise the clock to light and to social cues, respectively. The retino-hypothalamic pathway is especially intriguing because it contains projections from intrinsically photoreceptive retinal ganglion cells, which employ a novel photopigment melanopsin, and depolarise in response to light.[7] Although retinal rods and cones can contribute to circadian entrainment, they are not necessary for it. The dorsal shell of the SCN, typified by GABAergic neurons that co-express arginine vasopressin (AVP), is synchronised by the core neurons: loss of inter-neuronal signalling via the VPAC2 receptor for VIP (Figure 2b) desynchronises the population of clock cells.[8] Together, VIP and AVP-ergic projections from the SCN convey circadian signals, both directly and indirectly, to hypothalamic centres, the brain stem and spinal cord to control neuroendocrine and autonomic rhythms. Of especial interest in the context of sleep regulation are connections to the sleep centres of the ventral preoptic area and the orexin/ hypocretin neurons of the medial hypothalamus.[9]

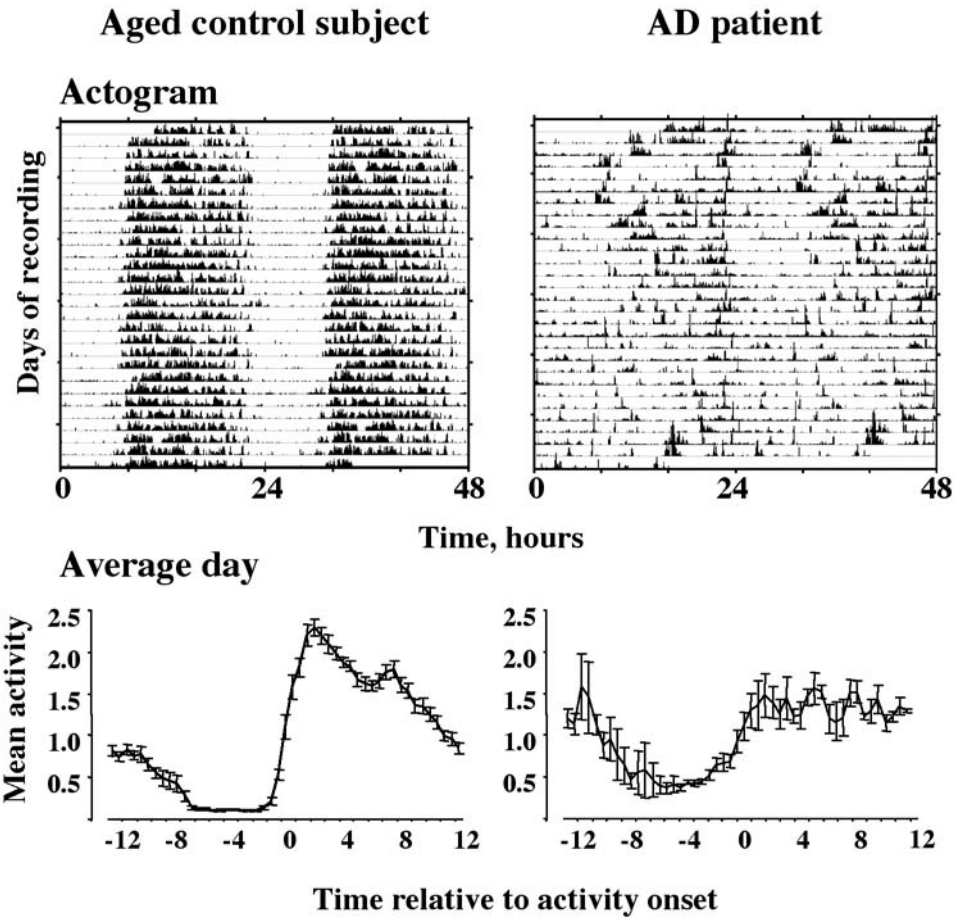

Figure 1: Disturbed rest/activity cycles in dementia
Rest/ activity records, obtained in home settings using wrist-worn activity meters, of representative healthy aged control subject and a patient with putative Alzheimer's disease (AD) with moderate dementia. Upper panels are daily records (actograms) plotted in 48 hour format for ease of inspection. Lower panels are graphical plots of the average daily cycle over the 4 weeks of recording. Note clear and robust 24 hour rhythm in age-matched control and loss of definition in patient, with nocturnal activity and loss of consolidated activity in daytime. Taken from reference 14.

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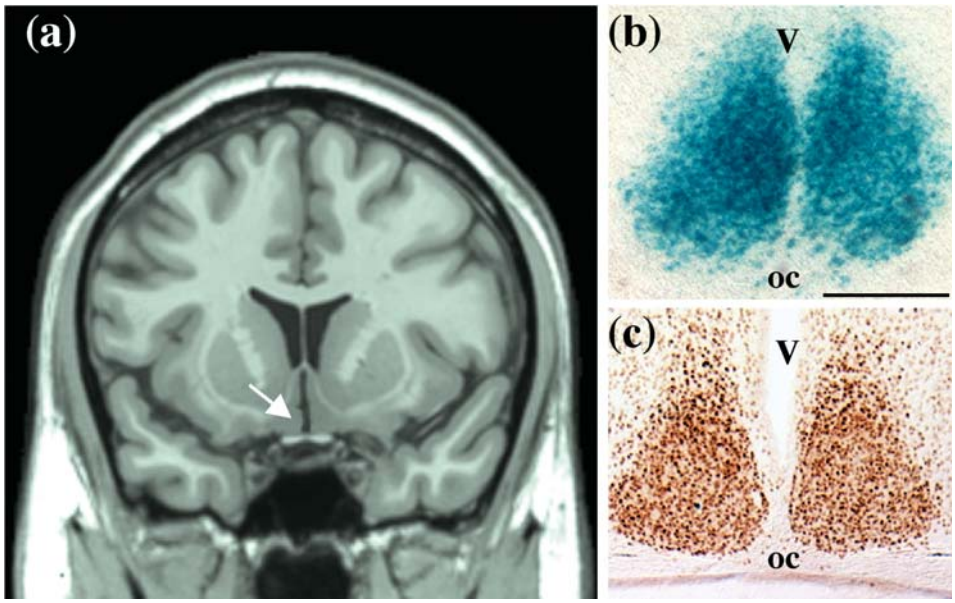


Figure 2: The suprachiasmatic nuclei as the brain's clockwork
(a) Frontal MRI scan of human to illustrate position of SCN (arrowed) at conjunction of optic chiasm and third ventricle. Image courtesy of Dr Adrian Owen, MRC CBSU, Cambridge.
(b) Frontal section of SCN from mouse carrying beta-galactosidase transgene as a reporter of the VPAC2 receptor for VIP. This neuropeptide receptor is widely expressed in SCN and is essential for circadian synchronisation of the clock cells. oc: optic chiasm, v: third ventricle, scale bar 500um.
(c) Frontal section of SCN from mouse immunostained for PER2 protein, a critical component of the molecular clockwork. At this stage of the circadian cycle, subjective dusk, almost all SCN neurons are expressing the PER2 protein in the nucleus where it negatively regulates Per2 and other circadian genes.

Clock genes

Clues to the molecular genetic machinery of the SCN clock came from mutagenesis screens in the fruit fly, which identified first period and then timeless as 'clock genes'. Following the identification of mammalian homologues of the fly genes and the de novo discovery of the Clock gene by mutagenesis in mice, expression and biochemical studies have established a model of mammalian clockwork based upon an auto-regulatory, negative feedback loop involving both transcriptional and post-translational events[10,11] (Figure 3a). In mammals, CRYPTOCHROMES (CRY) are the protein partners to PERIOD (PER). Expression of the two Cry and three Per genes is activated at the start of circadian day by transcriptional complexes containing CLOCK and BMAL proteins that act via E-box regulatory sequences on the Per and Cry genes. Towards the end of circadian day PER and CRY protein complexes accumulate in the nuclei of SCN cells (Figure 2c) and initiate the negative feedback phase, shutting off CLOCK and BMAL activity. Consequently, as PER and CRY are degraded and not replaced, their abundance decreases across circadian night, so that with the next circadian dawn the genes are released from negative feedback and the cycle able to restart. The stability, precision and amplitude of this cycle are enhanced by a secondary loop that involves two further rhythmically expressed proteins; RORA and REV-ERBα, which respectively activate and repress the Bmal gene. Their co-ordinated actions lead to rhythmic Bmal expression that peaks as Per and Cry expression reaches its minimum, thereby facilitating the initiation of the new cycle.

The molecular cycle is entrained by glutamatergic retinal afferents, which act via NMDA and AMPA receptors on SCN neurons to activate calcium dependent kinases, ultimately leading to induction of Per1 and Per2 genes. Under steady state conditions, marginal induction of Per by dawn or dusk light will trigger a small phase shift that entrains the clock to exactly 24 hours and so matches it to external time. Travel between time-zones demands shifts of up to 12 hours but the molecular apparatus is unable to accomplish this in one cycle. Hence 'jet-lag' arises as a mis-match between internal physiological time and the external world. Realignment of internal time proceeds at the rate of approximately 1 h per day, although molecular delays are more rapid than advances, hence the relative ease of westwards travel. The debilitating effects of rotating shiftwork also have a circadian basis. Not only is sleep sub-optimal because it is scheduled to occur when the internal clock is promoting the waking state (and vice versa), but also the internal physiology of a worker can be in a permanent jet-lag like state over the course of the shift rotation.

Circadian clock mutants in mice and people

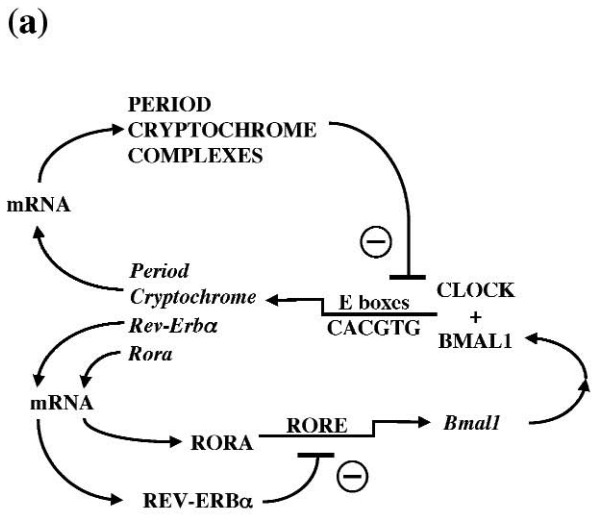
Because of the complex interactions within these feedback loops, mutations of the individual genes in mice are associated with various phenotypes.[1,11] An induced mutation of Clock compromises the trans-activating function of the encoded protein and lengthens circadian period from 23.5h in wild-type to 27-28h in the homozygote. Targetted knock-out of Bmal makes mice behaviourally arrhythmic, as does loss of Per2. In contrast, loss of Per1 destabilises circadian behaviour but loss of Per3 has little effect on rest/activity cycles. Loss of both Cry genes also leads to arrhythmicity, probably because in the absence of CRY proteins, PER2 protein is destabilised. Indeed, the stability of PER proteins appears to be a critical feature of the feedback loop, and phosphorylation plays a pivotal role in this. Studies in Drosophila have revealed that several kinases, including two casein kinases, phosphorylate Per and target it for proteosomal degradation, and that mutations to the kinases and associated ubiquitin ligase complexes alter circadian period and/ or stability. In the Syrian hamster, a spontaneous mutation in the gene encoding casein kinase 1ε dramatically accelerates circadian period to 20h in the homozygote. Changes in PER stability also have marked consequences in some people. Familial advanced sleep phase syndrome (FASPS) is a rare condition characterised by severely advanced sleep/wake cycles and circadian period of ca. 21- 22 hours. It arises from mutations of critical phosphorylation sites in the casein kinase-binding domain of human PER2 protein,[11] or a mis-sense mutation in the kinase itself.[12] More generally, length polymorphisms in the Per3 gene have been associated with evening and morning preference in the wider population.[13]

Real-time imaging of circadian timing in SCN

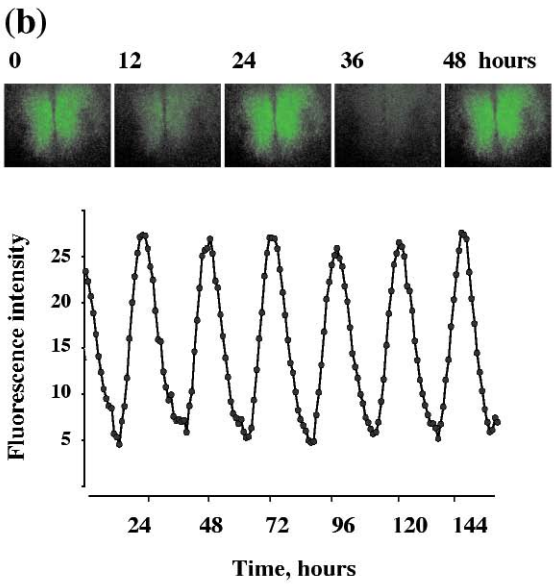
A major new technical development that has revolutionised our appreciation of the intrinsically dynamic nature of circadian mechanisms has been the advent of real-time imaging of circadian gene expression. Using organotypic SCN slices from rodents carrying fluorescent or bioluminescent reporter transgenes driven by circadian promoter sequences, it is now possible to observe the molecular clockwork 'ticking' through its cycle (Figure 3b). The most pronounced molecular cycles are concentrated in the AVP-rich region of the SCN shell. Under normal conditions the cell population is tightly synchronised, Per expression peaking in the circadian day with the medial neurons phase-leading by two to three hours. The remarkable precision and autonomy of this molecular timekeeper is emphasised by its persistence in organotypical SCN slices maintained in culture for many months: this is no feeble clock! Intercellular communication is, however, critical for normal function. Treatment with TTX to block Na^+-dependent action potentials immediately suppresses the amplitude of circadian gene expression, and over several days the population of rhythmic cells becomes desynchronised. A comparable loss of amplitude and desynchrony is seen in mice lacking the VPAC2 receptor for VIP, emphasising the role of SCN neuropeptidergic signals in sustaining intra-cellular timing.[8]

Circadian timing in peripheral tissues

As noted above, most physiological processes exhibit circadian modulation and in particular pathologies, most notably cardiovascular disease; this translates into a circadian prevalence of morbidity and mortality.[1] Such circadian co-ordination lies in temporal programming of gene expression, as revealed by micro-array based transcriptomic analyses, and also circadian co-ordination of the proteome. Until recently, the prevailing view was that exclusively SCN-dependent signalling drove these peripheral cycles. Real-time recording of circadian gene expression has now shown that many peripheral tissues, including heart, liver and kidney contain their own local clockwork, based on the same molecular feedback



(a) Schematic model of the feedback loops thought to underpin circadian timing in SCN neurons and other rhythmic cell types. Period and Cryptochrome are the principal genes mediating negative feedback. The cycle is stabilised by a secondary loop involving two orphan nuclear receptors, RORA and REV-ERBα which, respectively, activate and suppress expression of Bmal thereby timing the onset of activation to Per and Cry by CLOCK/BMAL complexes. The activity of clock-output genes will be timed by the rhythmic abundance and accumulation of PER, CRY, RORA and REV-ERBα and their dependent factors. See text for further details.



(b) Real-time recording of circadian fluorescence emission from organotypic SCN slice of Per1::dsGFP transgenic mouse. Upper panels are serial frames (every 12 hours) from the slice showing cellular rhythms of gene activity. Lower panel is graphical plot of relative intensity of fluorescence (grey scale units) integrated over the region of the left SCN every hour. Note precise ca. 24 hour timekeeping over the course of the study, with peak expression defining circadian daytime and the nadir circadian night.

loops as in the SCN. The SCN are now viewed as a co-ordinator of these local clockworks rather than a primary driver of peripheral rhythms. Internal synchronisation is dependent on multiple redundant pathways, including corticosteroid secretion and metabolic cues related to feeding schedules. The SCN hold a privileged position because they are the sole entry point of photic information into the system, and because they directly or indirectly control the internal synchronising cues. Experimentally, for example with restricted feeding schedules, the link between SCN time and peripheral clocks can be broken. The prevalence of cardiovascular and gastrointestinal disease in long term-shift workers may be related to metabolic dysfunctions caused by inappropriate meal-times. Granny's dictum that regular sleep and three regular daily meals is the key to a long and happy life may well have circadian truth behind it.

Circadian disorder in neurological disease

The incidence of sleep disorders, many of unspecified origin, increases with age, especially above 60 years. Many will not have a circadian origin, although in a few definitive cases such as FASPS, mutations of the molecular clockwork are clearly causal in disrupting the sleep pattern. The circadian timing of sleep in the healthy elderly is robust, even if the duration or quality of sleep is disappointing. Equally, in aged rats the molecular oscillator of the SCN, as reported by Per-dependent luciferase emission, is perfectly competent when isolated in culture. In neurological conditions, especially Alzheimer's disease (AD) and Huntington's disease (HD), the situation may be very different. The progressive loss of daily organisation to the sleep-wake cycle in AD and the problems this causes for patient care in a home setting is the principal cause of institutionalisation, with its incumbent personal, social and economic costs (Figure 1).[14] In AD, it remains unclear as to whether the central timekeeper of the SCN is compromised. Some dependent rhythms such as core body temperature show alterations of phase and/ or amplitude, but are essentially rhythmic, as is cortisol secretion. The sleep disorder may therefore reflect a disturbance in signalling between the SCN clock and centres controlling sleep and arousal, or an inability within the cerebral cortex to sustain a sleeping and/ or waking state. Nevertheless, effective management of the sleep disruption, for example by enhanced environmental cues (nocturnal darkness, bright daytime light, regular meals), could benefit patients and carers.[15] Moreover, nothing is known of the peripheral clock functions in AD patients: are they running normally or are they and their dependent metabolic cycles compromised, leading to a general malaise?

Sleep disorder is also recognised in HD. Again this may be multi-factorial, but direct evidence for a circadian basis comes from transgenic mouse models, which recapitulate the disorder of increased activity during the normal sleep phase, blurring the behavioural distinction between day and night.[16] Moreover, circadian gene expression in the SCN of these mice is normal when they are pre-symptomatic but becomes severely blunted as the rest/activity pattern breaks down. It remains to be determined whether disturbance of the molecular time-keeper arises from altered sleep patterns, or actually causes the behavioural abnormality. As with AD, neurodegeneration may compromise the transmission of circadian cues to sleep centres and/ or the forebrain. The general point nevertheless remains that effective management of 24 hour behaviour would benefit both patient and carer, even if the progression of the disease can not be curtailed.

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The Rotigotine Transdermal Patch May Provide Continuous Dopaminergic Stimulation in Early-Stage Parkinson's Disease

Parkinson's disease is a common disorder. Estimates of the prevalence of Parkinson's disease in Europe vary from 65–1250 per 100,000 people, with the variations possibly due to environmental or genetic factors or as a consequence of methodological differences or variation in age distribution between studies.[1] Similarly, estimates of the incidence of Parkinson's disease range from five to 346 cases per 100,000 people per year.[1]

Parkinson's disease is characterised by motor symptoms, particularly bradykinesia and rigidity, which are attributed primarily to dopamine depletion after loss of neurons from the nigrostriatal pathway.[2] However, progressive loss of other neuronal pathways, including serotonergic, noradrenergic and cholinergic systems, also contributes to the pathology of this disorder.[3] The resulting motor disability, together with the frequent presence of non-motor features such as depression and cognitive impairment, progressively impacts activities of daily living.[4] In the absence of clinically proven disease-modifying drugs, there is a need for convenient therapies with long-term efficacy in controlling the symptoms of the disease.

Limitations of current therapy

Levodopa

Almost 35 years after its introduction, levodopa remains the mainstay of therapy for Parkinson's disease. Levodopa is generally administered orally and is absorbed in the small bowel. This sometimes presents problems for patients with swallowing difficulties. The short half-life of levodopa necessitates multiple doses, typically commencing with three doses per day and increasing gradually to up to 10 daily doses. Having to take many tablets each day is associated with erratic timing of medication and poor adherence.[5]

Levodopa is routinely administered in combination with a dopa decarboxylase inhibitor, such as carbidopa, to prevent peripheral decarboxylation, improve availability to the central nervous system (CNS) and minimise peripheral dopaminergic side-effects. The catechol-O-methyltransferase (COMT) inhibitors entacapone and tolcapone are used primarily to prevent peripheral breakdown of levodopa and maximise its effect in the CNS. Entacapone can cause diarrhoea,[6] and tolcapone requires extensive liver monitoring and is reserved for severe cases.[7] The COMT inhibitors are therefore used as an adjunct to levodopa only after motor complications begin to emerge. Monoamine oxidase-B inhibitors (MAOBI) also prevent the breakdown of levodopa and dopamine. However, preventing dopamine breakdown through enzyme inhibition (such as with MAOBI) is inherently likely to offer lower efficacy than supplementation with a new substrate (such as with levodopa or dopamine agonists).

Although levodopa is initially effective in Parkinson's disease, motor fluctuations inevitably

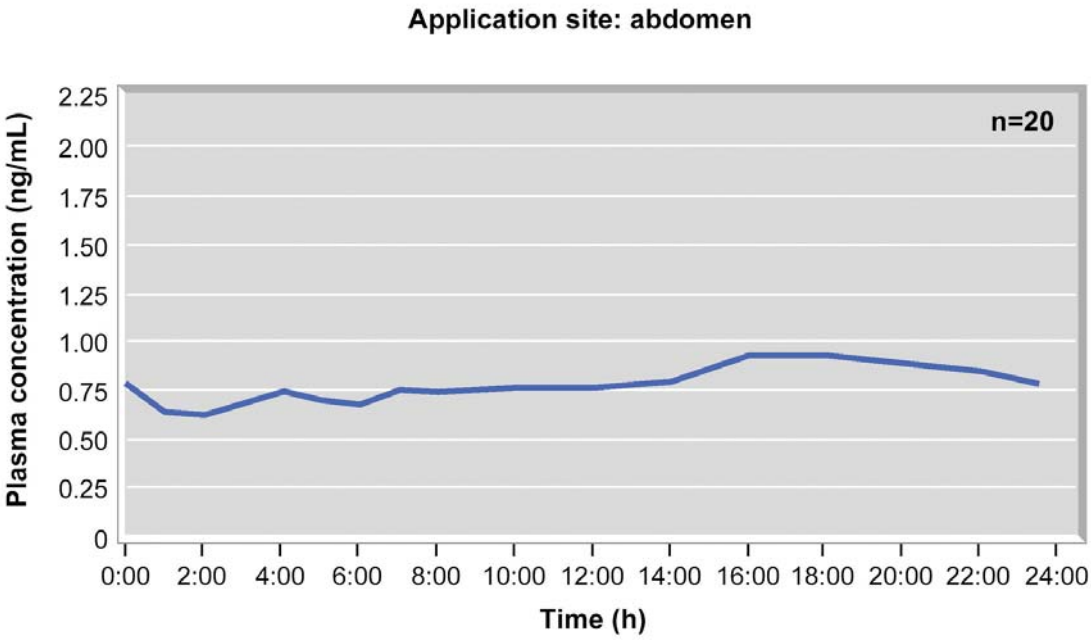
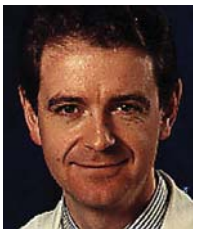


Figure 1: Mean steady-state plasma concentration during repeated daily administration of rotigotine 2mg/24h transdermal patches in patients with early-stage Parkinson's disease. Combined pharmacokinetic data from two days are shown. Data from the abdominal application site are presented; similar profiles were observed for other application sites (shoulder, upper arm, flank, hip, thigh; data presented at the *9th Congress of the European Federation of Neurological Societies*, 17-20 September 2005). Reproduced with permission from SCHWARZ PHARMA.



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His ongoing clinical and research interests are in Parkinson's disease and movement disorders. He is director of the Regional Movement Disorder Clinic, a co-founder of the Glasgow Movement Disorder Group, and also runs the Regional Dystonia Clinic.
In Parkinson's disease his research is currently focused on diagnostic techniques for Parkinson's disease and therapeutic compliance. Novel approaches to prevention and management of fluctuations and dyskinesia are being explored. These clinical treatment angles reflect his dual training in clinical pharmacology and neurology.

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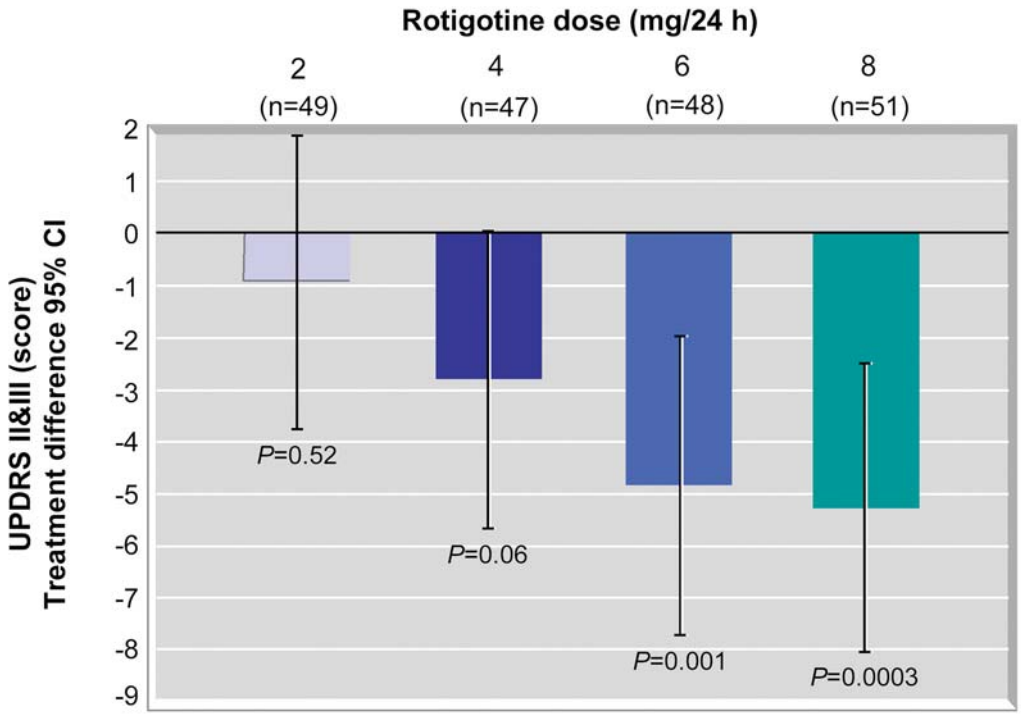

Figure 2: Adjusted treatment difference (difference in mean change between an active treatment group and the placebo group adjusted for the baseline value) for the activities of daily living (part II) and motor (part III) UPDRS scores at week 11 in the phase II trial of rotigotine monotherapy in early-stage Parkinson's disease. Data from the Parkinson Study Group, 2003.[24] Figure reproduced with permission from SCHWARZ PHARMA.

emerge. Motor complications ('wearing off' and 'on-off' fluctuations) typically develop after four to six years of disease duration and affect most patients within 10 years.[8,9] Pulsatile stimulation of dopamine receptors is considered important in this process.[10] There is experimental evidence to suggest that frequent levodopa dosing, in combination with a COMT inhibitor, may reduce pulsatile stimulation and reduce motor fluctuations. For example, in a model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), treatment with levodopa plus carbidopa twice or four-times daily produced similar levels of motor fluctuation and dyskinesia.[11] However, co-administration of levodopa and entacapone four-times daily reduced fluctuations and lessened dyskinesia.

Dopamine agonists

Dopamine agonists are often used as a first-line treatment option because they delay the onset of motor fluctuations and dyskinesia.[10] Dopamine agonists generally have longer half-lives than levodopa and thus stimulate receptors for longer, reducing peaks and troughs. Nevertheless, many dopamine agonists have half-lives of less than 12 hours, and require multiple daily oral doses. The dopamine agonist cabergoline has a relatively long half-life (>24 hours), but, in common with other ergot-derived agents, is associated with potentially severe fibrotic reactions.[12] To reduce the risk of fibrotic reactions, non-ergot dopamine agonists are preferred.[10]

The need for continuous dopaminergic stimulation

In healthy individuals, striatal dopamine receptor activation remains relatively constant.[10] Therapies that provide non-pulsatile continuous dopaminergic stimulation (CDS) may be able to prevent the development of motor complications in early-stage Parkinson's disease, or reverse motor complications if initiated in late-stage disease. Studies with continuous infusion of levodopa or dopamine agonists support the hypothesis that continuous stimulation reduces the risk of motor complications.[13,14] However, continuous infusion is expensive and impractical for most patients. Sustained-release preparations of levodopa have shown no advantages in terms of postponing or preventing long-term motor complications compared with immediate-release formulations,[15,16] probably because the increase in effective half-life is insufficient to overcome pulsatile stimulation.

The rotigotine transdermal patch

Transdermal delivery is a potential solution to providing continuous drug delivery for patients with Parkinson's disease. Rotigotine is a non-ergot, selective D3/D2/D1 dopamine agonist[17] that can be delivered transdermally due to its high lipid solubility. Rotigotine resembles dopamine structurally and has a similar receptor profile, with significant D1 receptor activity. In contrast to ergot-derived dopamine agonists, rotigotine has minimal 5-HT_{2B} activity, and therefore has a low risk of inducing fibrosis and cardiac toxicity.[18] Rotigotine also has agonist actions on 5-HT_{1A} receptors and antagonist actions on α_{2B} receptors, which may theoretically contribute to other beneficial effects, such as antidyskinetic activity and antidepressant action,[19,20,21] although this has yet to be evaluated in clinical trials.

The rotigotine transdermal patch contains the drug in a silicone adhesive, which is spread evenly across a foil backing. This configuration provides uniform release of the drug at a constant rate, such that drug delivery is directly proportional to patch size and gives stable plasma drug levels over 24 hours (Figure 1). Microdialysis studies showed that constant plasma levels of rotigotine resulted in constant dopaminergic stimulation (as demonstrated by persistent decreases in extracellular dopamine, which indicate constant stimulation of presynaptic dopamine receptors).[22] Further experimental investigation showed that CDS by rotigotine had a very low propensity to induce dyskinesias.[23]

Clinical efficacy in early-stage Parkinson's disease

The rotigotine transdermal patch was evaluated in a randomised, double-blind, placebo-controlled, phase II study of 242 patients with early-stage Parkinson's disease.[24] Patients received patches containing 4.5, 9.0, 13.5 or 18.0mg of rotigotine (equivalent to delivered doses of 2, 4, 6 or 8mg/24h) or placebo for 11 weeks. A dose-dependent improvement in Unified Parkinson's Disease Rating Scale (UPDRS) II and III scores between baseline and week 11 was observed, with the improvement being significant (P≤0.001) for the 6mg/24h and 8mg/24h dose groups (Figure 2).

These promising results were confirmed in a phase III study of 302 patients with early-stage Parkinson's disease.[25] Patients received an initial dose of rotigotine 2mg/24h (or placebo), which was titrated weekly in 2mg/24h increments to an optimal response or a maximum of 6mg/24h, which was then continued for a further 24 weeks. Patients who received rotigotine had significant improvements in UPDRS II and III scores at the end of treatment (mean improvement of –4.0 points compared with a worsening of +1.3 in the placebo group; P<0.0001), and there was also a significantly greater response rate (percentage of patients with ≥20% reduction from baseline in UPDRS II and III) for patients treated with rotigotine than for patients who received placebo (47.5% vs 18.8%; P<0.0001).

Safety and tolerability

Adverse events from the rotigotine transdermal patch were similar to those of other dopamine agonists,[26,27] including headache, dizziness, nausea, vomiting and somnolence.

One potential disadvantage of transdermal drug delivery is the potential for application-site reactions. In clinical trials, the rotigotine transdermal patch was associated with an incidence of application-site reactions of 39%[24] and 44%,[25] although only a small subset was severe. This means that a small number of patients are unable to continue using the rotigotine transdermal patch (around 4–5% in clinical trials discontinued because of application-site reactions). The risk of skin reactions is reduced by daily rotation of the application site, and there is evidence of a lower rate of skin reactions when the rotations are strictly undertaken.

Summary

Rotigotine is the first dopamine agonist to be delivered successfully by transdermal application, and offers a new option for patients with early-stage Parkinson's disease. Continuous drug delivery from transdermal application of rotigotine provides stable plasma drug levels over 24h. This should translate into continuous, non-pulsatile dopaminergic stimulation, which could be beneficial in delaying long-term motor complications.

Rotigotine is the first dopamine agonist to be delivered successfully by transdermal application, and offers a new option for patients with early-stage Parkinson's disease

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Orthoses in the Management of Spasticity in the Lower Limb

Introduction

Lower limb spasticity is commonly seen in stroke, spinal cord injury, traumatic brain injury, multiple sclerosis and cerebral palsy. It commonly occurs with other neurological features such as muscle weakness, loss of muscle control and loss of sensation.

As in all other aspects of rehabilitation, there must be a multidisciplinary approach to its management. Adequate assessment of the specific impairments causing disability is necessary for appropriate interventions to be instituted.

The orthotist has a key role in advising about appropriate orthotic devices that can be used in a particular patient, prescription and manufacture of the orthosis as well as undertaking regular reviews to ensure that it continues to meet the patient's needs. In referring patients, the clinician must provide enough clinical detail and aim of referral to help the orthotist provide the most appropriate device.

Orthoses are generally used in conjunction with other interventions including physiotherapy, positioning, stretching, oral antispasticity medication and botulinum toxin injections.

Orthoses

Orthoses are external devices designed with the aim to affect body function and/or assist function.[1] They may be prescribed in patients with lower limb spasticity with the aims of:

- Decreasing muscle spasticity by increasing muscle length through providing a prolonged stretch and exerting an inhibitory effect through sensory stimulation.
- Breaking up mass patterns of movement
- Improving biomechanics and improving stability

Use of orthoses may create problems by serving as a resistance against which the patients' spasticity is exacerbated, causing immobilised muscles to atrophy or increasing spasticity in more proximal muscles.[2] Impaired sensation increases risk of pressure ulceration.

Specific Orthoses

Ankle contracture boots

These are useful for management of mild to moderate spasticty and contracture at the ankle especially in non-ambulating patients. They provide a stretch by means of a foot positioner, adjustable for various degrees of plantiflexion, straps to vary inversion and eversion and a cut-out in the lining foam to protect the heel and prevent pressure ulceration. Some versions incorporate an ambulation pad. A commercially available example is the Leeder Multi Use Boot (Medistox Ltd) (Figure 1).

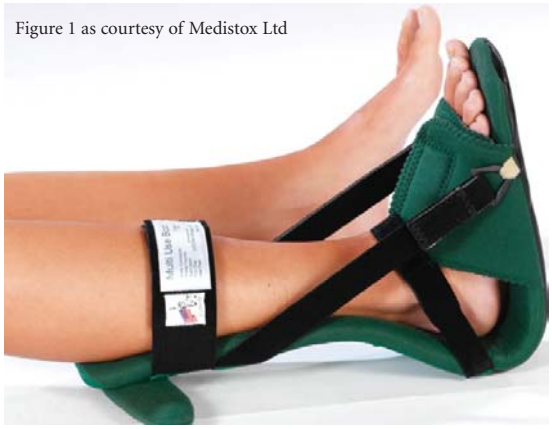

Figure 1 as courtesy of Medistox Ltd

Ankle-Foot Orthoses (AFOs)

These are commonly prescribed for patients with lower limb spasticity to help substitute for inadequate muscle function during key stages of the gait cycle, optimise alignment and manage abnormal muscle tone.[3,4]

AFOs range from off-the-shelf to custom-made and are commonly made of carbon fibre (ToeOFF™ splint) (Figure 2) or plastic. They may be articulating to allow sagittal plane movement at the ankle. Various features may be incorporated in them to help manage specific problems which are identified during the assessment process. A description of the huge range of AFOs is beyond the scope of this article but some specific examples are mentioned below:

- A dynamic ankle-foot orthosis (DAFO) (Figure 3) is a very thin flexible supramalleolar orthosis with a custom contoured sole plate to include support and stabilisation of the dynamic arches of the foot.[5] DAFOs are commonly used in the paediatric population, especially in children with cerebral palsy.

- Some children with diplegic cerebral palsy have weakness in the quadriceps and ankle plantarflexors and walk with excessive knee flexion and ankle dorsiflexion (crouch gait). This may be corrected by use of a rear entry ground reaction AFO which creates an extending moment at the knee to help produce a more upright gait.

- The Thonnissen support (Röck Orthopädie) (Figure 4) is an articulating carbon fibre AFO with adjustable elasticated dorsiflexion assist straps which allows greater range of movement at the ankle than a standard ToeOFF™ splint.

- In comparing metallic and plastic AFOs, Gok et al[6]

Figure 2

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Figure 3

found that metallic AFOs were better at increasing ankle dorsiflexion angles. They concluded that these provided better stabilisation at the ankle, improving heel strike and push-off.

- Evidence of the efficacy of AFOs in children and adults is inconclusive. Most studies have used small numbers of patients with no long term follow up. Morris[7] in a review concluded that the efficacy of orthoses to help in overcoming functional limitations and preventing contractures (in cerebral palsy) remains to be established. Likewise Leung and Moseley[3] highlighted the lack of large well designed studies of their efficacy in hemiplegic adults.

Contracture Correction Devices

Contracture refers to shortening of muscle with reduced passive range of movement as a result of prolonged maintenance of muscle in a shortened position.[8] It frequently occurs as a result of inadequately treated spasticity.

Serial casting is frequently used in the management of contracture. In this a cast is applied over the affected joint and periodically changed to increase the stretch on the affected muscle, decreasing tone and leading to increase in range of movement.

Contracture correction devices have been developed as an alternative to serial casting. They essentially consist of a hinged orthosis which spans the affected joint to which a mechanism for applying a continuous but adjustable

Figure 4

level of stretch by means of a coil spring, gas spring or clockwork spring is attached.[9] The tension in the device can be set so that it can be overcome eg by a spasm. In one trial, knee contractures were reduced by an average of 10.7° in four weeks.[10]

One commercially available version is the Advance Knee Brace (Technology in Motion Ltd) (Figure 5). Advantages of this over casting include decreased staff time spent in recasting, ability to provide an accurate amount of stretch, ease of skin inspection to minimise risk of pressure ulceration and ease of fitting. Some devices may be refurbished for re-use potentially reducing costs in the long term.

Tone inhibiting insoles

In some patients hyper-extension of the hallux may lead to difficulty or discomfort in walking. For such patients a bar made of firm sponge rubber and on a flat insole base may be placed proximal to the metatarsal heads. This has the effect of offloading the metatarsal heads and encouraging plantar-flexion of the hallux, relieving pain and build up of callus under the head of the first metatarsal. This may be used in conjunction with Botulinum toxin injections to the extensor hallucis longus to reduce tone.

In the published literature Iwata et al[11] have described the use of an inhibitor bar placed distal to the metatarsal heads on an AFO. This has been shown to improve the walking ability of hemiplegic patients with tonic toe flexion reflex.

Conclusion

As in all other aspects of rehabilitation, a multidisciplinary approach is essential for the management of lower limb spasticity. There exists a huge range of orthotic appliances, including various types of AFOs for management of spastic equinus/equinovarus deformity at the ankle, contracture correction devices and tone inhibiting insoles. The input of an experienced orthotist is invaluable in assessment and selection of the appropriate orthosis, however adequate clinical information and aim of referral should be provided to facilitate this.

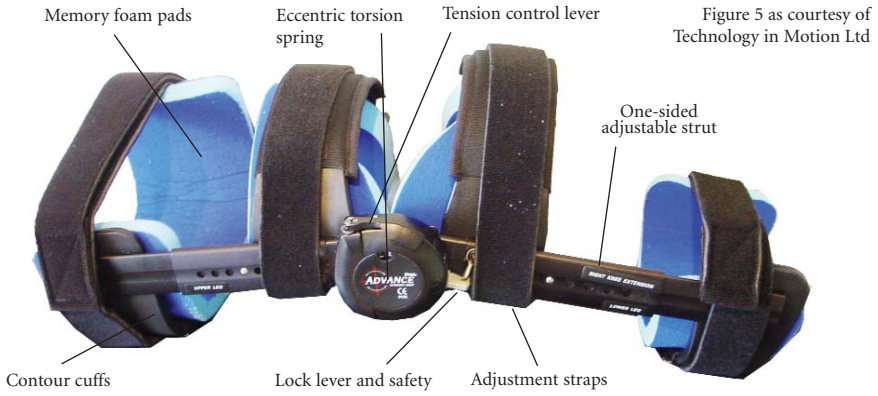

Figure 5 as courtesy of Technology in Motion Ltd

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www.medistox24.com - Medistox Ltd
www.roeck.de - Röck Orthopädie

'Neurological Literature' - Headache (Part 2)

The Oxford English Dictionary defines headache as:

> An ache or continuous pain, more or less deep-seated, in the cranial region of the head.

Compared with the richness and variety of definition to be found in the IHS classification of headache,[1] the OED seems a little prosaic.

Although accounts recognisable as descriptions of migraine may be found in the remaining works of several ancient civilizations,[2] the earliest reference to headache acknowledged in the OED comes from a Saxon document of ca. 1000 AD, followed by a quote from a work of John de Trevisa dated 1398:

> Also heed-ache cometh of grete fastinge and absty-nences

The first literary reference to headache mentioned in the OED is from 1581, Sir Philip Sidney's (1554-1586) *An apologie for poetrie*:

> How many head-aches a passionate life bringeth us to

Not mentioned in OED, but perhaps the first literary work devoted to headache is a poem of 1648, entitled *The Head-ake* by Robert Herrick (1591-1674), in his collection *Hesperides* (H-591):

> My head doth ake,
> O Sappho! take
> Thy fillit,
> And bind the paine;
> Or bring some bane
> To kill it.
>
> But lesse that part,
> Then my poore heart,
> Now is sick:
> One kisse from thee
> Will counsell be,
> And Physick.[3]

One wonders whether this might be an example of art imitating life: did the author's experience of headache prompt the writing of the poem? [There is another possible reference in one of Herrick's poems entitled *Upon Love*, H-509: I held Love's head while it did ake;/But so it chanc't to be;/The cruell paine did his forsake,/And forthwith came to me.[3]] A similar question may be addressed to the many writers who have mentioned headache in their works, some of which have already been documented.[4] For example, did Charles Lutwidge Dodgson's headaches influence the pseudonymous Lewis Carroll's depictions of Alice in Wonderland?[5] Seldom can this question be definitively answered, although Vlad Zayas has skilfully traced the possible links between the character Pontius Pilate's headaches in *The Master and Margarita* and the author Bulgakov's (1891-1940) headaches.[6]

Herrick's poem is quoted in full in one of his earliest extant letters (November 1898) by the American writer Jack London (1876-1916).[7] Interestingly, headaches crop up in several of London's books: *The People of the Abyss* (1903; chapter 21, describing the effects of industrial white lead poisoning in the East End of London); *The Sea-Wolf* (1904; chapters 10,13,33); and *The Iron Heel* (1908; chapters 23,24), in both the latter afflicting London's characters. Did London himself suffer from headaches? Only three mentions of headache are to be found amongst the largest published collection of his letters (1557 in all), occurring in the context of other systemic illness (fever, cold) or on a boat in driving wind and snow; in the latter he was "nearly blind with a headache" (is migraine a possibility?).[7] Even in the autobiographical *John Barleycorn or, Alcoholic Memoirs* (1913), there is no mention of headache per se, although following the consumption of wine at the tender age of seven London reports "The alcohol I had drunk was striking my … brain like a club".[8]

Another American author aware of headaches was Louisa M Alcott, as exemplified in her novel *Little Women, or Meg, Jo, Beth and Amy* (1868).[9] Three of the four young ladies are afflicted at one time or another; only Amy, aged 12, seems unaffected (pre-menarche?). Beth, aged 13, has headaches which force her to lie on the sofa and cuddle her cats; headache is also the first symptom of the scarlet fever from which she becomes delirious. Jo (16) has had a headache which is ascribed to reading too much, although of note this occurs when her usual daily routine of looking after a trying elderly relative, Aunt March, comes to an end and the 'experiment' of not working is tried. Like London, Alcott also recognises the perils of alcohol: Meg (17), despite warnings from the girls' neighbour, Laurie, develops headache after drinking champagne.[9]

This latter example may fulfil IHS criteria for "Alcohol-induced headache immediate",[1] as may Jack London's boyhood experience with wine. Are young people, perhaps sampling alcohol for the first time, particularly susceptible? Another possible example occurs in *The Amber Spyglass*,[10] the third book in Philip Pullman's trilogy *His Dark Materials*, when young Will Parry is treated to vodka by Semyon Borisovitch. In a short story entitled *The man who liked Dickens* (1933), Evelyn Waugh, himself no stranger to the effects of alcohol, has the character Henty ("a shadowy version of [Waugh] himself") wake with a headache after drinking *piwari*, a local South American brew, so missing his chance to escape from the jungle and from McMaster, the man who likes Dickens but who cannot read and hence wishes Henty to remain permanently to read him the novels.[11]

Ian McEwan has made a name for himself in medical circles with his accounts of the life and thought of a neurosurgeon (*Saturday*, 2005) and of De Clerambault's syndrome (erotomania) (*Enduring Love*, 1997). In *Atonement*,[12] the matriarch Emily Tallis suffers from "the beast migraine":

> She was not in pain, not yet, but she was retreating before its threat. There were illuminated points in her vision, little pinpricks, as though the worn fabric of the visible world was being held up against a far brighter light. She felt in the top right corner of her brain a heaviness, the inert body weight of some curled and sleeping animal; but when she touched her head and pressed, the presence disappeared from the coordinates of actual space. … It was important .. not to provoke it; once this lazy creature moved from the peripheries to the centre, then the knifing pains would obliterate all thought … It bore her no malice, this animal, it was indifferent to her misery.

As for the pain: "At worst, unrestrained, a matching set of sharpened kitchen knives would be drawn across her optic nerve, and then again, with a greater downward pressure, and she would be entirely shut in and alone". This is set in 1935, and no specific treatment is mentioned. But is it purely chance that one of the plants growing in the cracks

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between the paving stones on the terrace is feverfew, sometimes prescribed as a prophylactic?

As a consequence of her migraine, Emily has developed an "expertise born of a thousand headaches, avoiding all things sudden or harsh", wearing dark glasses before going outside to fetch her daughter, and has "learned her patience through years of side-stepping migraine". Nonetheless, when unforeseen trouble comes, "she rose to the crisis, free of migraine and the need to be alone". The migraines also impact on the family: "As children they claimed to be able to tell from across the far side of the park whenever their mother had a migraine by a certain darkening at the windows." Her daughter avoids troubling her mother, since "nothing but migraine would have come of it". At another time, they see the migraines as "a comic interlude in a light opera".

McEwan is perhaps less secure in a later description, which purports to be of vascular dementia. A seventy-seven year old woman reports:

> My headaches, the sensation of tightness around the temples, have a particular and sinister cause. He [the doctor] pointed out some granular smears across a section of the [brain] scan. … I was experiencing, he said, a series of tiny, nearly imperceptible strokes. The process will be slow, but my brain, my mind, is closing down. … I have vascular dementia, the doctor told me … it's not as bad as Alzheimer's, with its mood swings and aggression.

Yet later she reports, "I fell asleep again and when I woke … a painful tightness was around my forehead. I took from my handbag three aspirins which I chewed and swallowed with distaste. Which portion of my mind, of my memory, had I lost to a minuscule stroke while I was asleep?"

Surely these are tension type headaches, possibly medication overuse headaches (waking from sleep, excessive analgesic consumption) and the scan appearances entirely incidental and appropriate for age? Has this fictional doctor (or possibly McEwan's source) had any training in the disciplines of headache or cognitive disorders? It is surprising that the careful research done for the historical parts of the book is not matched when it comes to medicine. Artistic licence, no doubt; the need for melodrama, possibly.

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Nobel Laureate launches £10m Brain Centre

Cardiff University's Brain and Repair Imaging Centre (CUBRIC) has been heralded as a development of international significance to Wales. The Centre was officially launched by Professor Sir Peter Mansfield, Nobel Laureate for Medicine in 2003, who pioneered the development of MRI scanning techniques that use a strong magnetic field to reveal internal organs and other tissues in extraordinary detail.

Speaking at its launch, the Minister for Education and Lifelong Learning, Jane Davidson, described the facility as world-class. She said that in addition to bringing real benefits in the understanding and treatment of disease it will further contribute to the international standing of the School of Psychology and of Cardiff University.

"Cognitive neuroscience is one of the most significant areas of contemporary science," she said. "This is a world-class offering and it will attract additional world-class researchers. Let's celebrate this fantastic new Centre."

Welcoming the new Centre, Vice-Chancellor, Dr David Grant said, "I congratulate Professor Peter Halligan and his colleagues on the opening of CUBRIC which puts Cardiff, and Wales, at the international forefront of developments in brain imaging. This is a significant development for the University and confirms our commitment to invest in areas of research which draw on recognised strengths right across the breadth of our academic schools."

Under the leadership of Professor Peter Halligan, CUBRIC will contribute to transforming the understanding of normal and damaged brain function, as well as to informing the treatment of brain impairments such as head injury, stroke, dementia and schizophrenia.

The distinctive focus of the Centre's research is aimed at understanding everyday cognitive (thinking), emotional and social processes, like how we learn a new skill, remember a face or solve a problem. Researchers will then be able to compare the damaged and healthy brain.

Funding of £10m combined with the appointment of two new Chairs (professors) and additional research staff will provide for a unique multi-disciplinary approach to understanding the structural, functional and theoretical aspects of brain mechanisms. The investment builds on existing strengths in several schools at Cardiff University to provide a world-class facility based around complementary applications of clinical and cognitive based research. This interdisciplinary neuroimaging program takes advantage of Cardiff's pre-eminence in neuroscience including neurobiology, cognitive neuroscience, psychology, computer science chemistry, clinical medicine, and translational research.

CUBRIC will be one of the few research-dedicated functional neuroimaging laboratories in the UK to have the latest brain scanning technologies, [3T Magnetic Resonance Imaging (MRI); and Magnetoencephalography (MEG)] in the same facility. For further information visit: www.cardiff.ac.uk/psych/cubric

EDITOR'S CHOICE

Multiple sclerosis

For years, Maria Marrosu has been producing quality research on the Sardinian population of people with multiple sclerosis and has shown how unusual they are, for instance in their HLA genetic susceptibility and associations with other diseases. This intriguing study may be her finest yet and with more universal significance.

The basis of their work was a fairly standard question: do relatives of people affected by multiple sclerosis have abnormalities that look like multiple sclerosis on MRI brain scans? Technically, this is straightforward to answer. The main difficulty of this sort of research is dealing with the 'normal' participants who turn out to have 'abnormal' scans; so the consent process incorporated a question asking whether participants wished to know the result of their scan. Two hundred and ninety-six people were examined and scanned (56 of whom were unrelated to someone with multiple sclerosis). The result was unsurprising. If you are a first-degree relative of one person with multiple sclerosis, there is a 5% chance your brain MRI will show white-matter abnormalities consistent with multiple sclerosis using the Fazekas criteria..... And if two or more people are affected by multiple sclerosis in your family, this risk goes up to 11%. The magnetisation transfer ratio (MTr) of individual white matter lesions in such people's MRI scans was low, indicating loss of cellular structure, just as is seen in regular multiple sclerosis lesions. An interesting question, not addressed in this paper, is: what happens to those 'normal' people with abnormal scans? It is important for what follows that they never develop multiple sclerosis.

The excitement of this work lies in some negative results: MRI brain volumes and MTr of normal appearing white matter were identical between all groups and also between those who did or did not have white matter MRI abnormalities. Yet both of these measures are consistently reduced in people with multiple sclerosis, reflecting the widespread loss of axons and myelin outside of the focal plaques, even early on in the disease.

Perhaps then, there is a two-hit pathogenesis of multiple sclerosis. Firstly, there are focal areas of inflammation, producing focal axonal and myelin loss. But the disease is only manifest in those individuals who then go on to develop widespread axonal loss and cerebral atrophy. This is not an original idea, but Marrosu's research has put it on a more secure footing. And of course it has important implications, not the least being that focusing our efforts on reducing focal inflammation in multiple sclerosis may not be the wisest move....And once again we are reminded that focal white matter lesions on a MRI scan do not necessarily cause any symptoms and do not mean that a person has multiple sclerosis. - ***AJC***

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ANNALS OF NEUROLOGY
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EPILEPSY: A hairy tale

★★★ RECOMMENDED

Serum blood levels give a snapshot of antiepileptic drug ingestion but do not tell much about AED compliance over time. The drugs are deposited in hair shafts as the hairs grow, at a rate of about 1cm per month, and so 1cm lengths of hair can be analysed for their content of AED to give a picture of the variability of drug ingestion. The authors looked at hair removed from four groups of patients at post-mortem: 16 possible or definite SUDEP; nine non-SUDEP deaths; 31 patients with epilepsy living in their own homes and 31 residents of the Chalfont Centre for Epilepsy, who were expected to have very consistent drug dosing. They created a measure of the variability of AED levels in the hair, with an adjustment for the number of hairs sampled. They found that this coefficient of variance was 20.5% (S.E. 1.5%) in SUDEP patients, 15% (S.E. 3.9%) in non-SUDEP patients, 9.6% in outpatients and 6.2% in Chalfont residents. One SUDEP patient had no detectable level of his prescribed AED anywhere in his hair. Whilst previous data regarding the risk of SUDEP and compliance have been contradictory, it has been shown before (not surprisingly) that patients with more frequent seizures are at increased risk of sudden death. This study does not control for seizure frequency but, with that caveat, it shows that compliance is an important factor in sudden unexpected death in epilepsy. So we need to explore the presence of, and reasons for, non-compliance more assiduously. - ***MRAM***

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2006; 77:474-80.

TRIPLET REPEATS: New Treatments?

There continues to be some controversy as to whether the formation of inclusions in cells in neurodegenerative disorders is a good or a bad thing for the neurons. A few years ago there was a great interest in developing drugs that have the potential to break down inclusions on the grounds that these may have some toxic function within the cells. Subsequently it appeared as though inclusion formation was an attempt by the cell to prevent cell death or at least was not causally related to its demise. As a result there has been a change in approach such that in a recent paper in the Proceedings of the National Academy of Sciences by Bodner et al they have used therapeutic approach which involves the promotion of inclusion formation. In this study the authors used alpha synuclein and huntingtin as their two mutant proteins in a number of cell lines and set about trying to use various agents to promote their aggregation into inclusions. They identified a number of compounds that could do this in their cellular models of both Huntington's disease and Parkinson's disease and comment that these compounds appear to reduce toxicity and thus may ultimately offer some benefit in the clinic. This is an interesting study, although is using a very artificial environment which limits its clinical significance. However it once more illustrates how in medical sciences subjects can be turned on their head in the space of a relatively short period of time. Of course we will now have to wait to see whether the trend reverses and inclusions become the perpetrator rather than the protector of cell death. - ***RAB***

Bodner RA, Outeiro TF, Altmann S, Maxwell MM, Cho SH, Hyman BT, McLean PJ, Young AB, Housman DE, Kazantsev AG.
Pharmacological promotion of inclusion formation: A therapeutic approach for Huntington's and Parkinson's diseases.
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
2006;103:4246-51.

EPILEPSY: Worms, twiddly volumetrics & wires in the head

About a quarter of all patients with epilepsy, close to 100,000 in the UK, will not respond to medication. Some of these can be treated surgically but most cannot. A key question is how to screen for those who will benefit. One potential strategy might be to scan patients and only put forward for surgery those patients whose scan shows a surgical target. However, according to this paper, that approach would miss some patients who would benefit from surgery. One hundred and thirty six patients had surgery, 105 of whom had implanted electrodes and 21 one of whom had normal neuroimaging. Three-quarters of patients, whether MRI positive or negative, were either seizure-free or nearly seizure-free at one year. The MRI studies were high resolution imaging with visual inspection but without volumetric measurements of the temporal lobes. Now every fisherman knows that what you catch depends on the bait. These authors argue that a 1.5 Tesla worm is all that you need but if you go a few miles across London you will find clinicians who think that if you use a 3 Tesla worm with twiddly volumetrics added, you will catch more fish. They will do many more clever scans and fewer electrode implantations. Are their patients comparable? Who knows! Perhaps they could challenge each other to a randomised trial of clever imaging versus wires in the head. So for the jobbing neurologist the debate moves on to who to refer from the group with normal routine MRI scans, even fewer of whom will benefit from surgery. The answer I believe comes down to good old clinical medicine. If the seizure type or the interictal or extracranial ictal EEG suggests a highly focal origin for serizures then your imaging has missed something. Either clever imaging will pick it up or you have to have wires in the head. Personally, I would go for clever imaging first and only have wires in the head later. - ***MRAM***

Alarcon G, Valentin A, Watts C, Selway RP, Lacruz ME, Elwes RDC, Jarosz JM, Honavar M, Brunhuber F, Mullatti, Salinas M, Binnie CD, Polkey CE.
Is it worth pursuing surgery for epilepsy in patients with normal neuroimaging?
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2006 Apr;77(4):474-80.

HEAD INJURY: Cage Fighting – athletes or assailants?

Some of you may wonder what exactly is Cage Fighting – I did too when first contacted by a BBC journalist a few weeks ago about a big 'cage fight' event in Manchester. This paper describes it's origins from 648BC when Pankration (Greek = All powerful) was featured in the 33rd Olympiad. It is also known as 'no holds barred' fighting, 'mixed martial arts' competition or extreme fighting. Basically, it involves two contestants, wearing minimal protective clothing, fighting (up to) three 5-minute rounds in a cage with a few limits such as no head-butting, biting or scratching/gouging etc. Apparently the cage is there to 'protect' participants from being thrown out of the fighting area. This paper is the first to systematically look at the health outcomes of this 'sport'. The author reviewed publicly available video footage of 1284 men in 642 consecutive televised matches in the US and Japan from 1993-2003 to determine the reason for the contest finishing (note the study was by a single author and no funding was declared). The single greatest reason for match stoppage was head impact (28%), followed by expired match time (27%), musculoskeletal stress (17%), neck choke (14%), miscellaneous trauma (13%) and disqualification (1%). Comparative figures of match stoppage due to head injury in boxing of 8.8% and kickboxing of 7.7% are given. The paper discusses the rules, equipment, stoppage classification and implications of the injuries (especially head) sustained. Three questions come to mind: Who are the 'expert doctors' at ringside? When are gladiators and duelling returning? Who is going to shout stop? - ***JMacF***

Buse GJ.
No holds barred sport fighting: a 10 year review of mixed martial arts competition.
BRITISH JOURNAL OF SPORTS MEDICINE
2006;40:169-72.

HEADACHE: Neck-tongue syndrome

★★★ RECOMMENDED

It is my hypothesis that every neurologist, even those especially interested in common disorders such as headache and epilepsy, has a (sometimes suppressed) passion for the obscure. This needs regular indulgence. Reading about neck-tongue syndrome fits the bill. This rare headache disorder consists of neck pain in the C2 distribution, coupled with ipsilateral tongue numbness, occurring during head rotation. The authors conducted a detailed headache survey and as part of this, looked for cases of neck-tongue syndrome. During a systematic epidemiological survey of 1838 parishioners of a community in Norway, four people with neck-tongue syndrome were identified. This gave a prevalence of 0.22% in this well-defined community group. None of the four had ever sought medical help for their condition. One subject had spasm of the tongue rather than numbness. Two also had ipsilateral cervicogenic headache at other times. Although the authors conclude that neck-tongue syndrome may be more frequent than previously thought, it is still pretty uncommon. Once encountered, it is hard to forget. Patients with it are likely to be pleased to have their syndrome recognised. Furthermore, it is a dramatic example of convergence of trigeminal and cervical sensory input, important in understanding mechanisms of headache. - ***HAL***

Sjaastad O, Bakketeig LS.
Neck-tongue syndrome and related (?) conditions.
CEPHALALGIA
2006;26:233-40.

MULTIPLE SCLEROSIS: and glandular fever

Over the years, proposed infectious triggers for multiple sclerosis have included (in historical order) syphilis, canine distemper virus, measles, human herpes virus 6 and chlamydia pneumonia. There has been increasing scepticism about the relevance of these observations, especially as it has been shown that polyclonal expansion of B lymphocytes is part of the immune defect in multiple sclerosis (Derfuss Brain 2001;124:1325-35.) However Epstein-Barr virus may be an exception. The elegant work of Lars Fugger's group (Nat Immunol 2002 Oct;3(10):940-3) has shown that there is sufficient sequence similarity between EBV and MBP to support molecular mimicry. And there has long been a clinical suspicion that EBV infection after childhood, to cause infectious mononucleosis or 'glandular fever', may predispose to multiple sclerosis. This has now been tested in a meta-analysis from this Boston team, which was so rigorous that 281 out of the 295 possible studies were discarded before the start! From the remaining 14 case-control and cohort studies, the relative risk of multiple sclerosis after glandular fever was calculated at 2.3 (95% confidence intervals 1.7-3.0). Under a model drawn up by the authors, individuals who had never been exposed to EBV (c.20% by serological tests in the UK), or those who had been exposed in childhood, had much lower risks of developing multiple sclerosis. The striking implication is that EBV vaccination might reduce multiple sclerosis frequency…

Regular readers of this section of ACNR will spot that this paper once again supports the 'hygiene hypothesis' of autoimmunity. It is clearly much better, at least as far as multiple sclerosis risk goes, to acquire EBV infection from a dirty childhood than from kissing at university! – ***AJC***

Thacker EL, Mirzaei F, Ascherio A.
Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis.
ANNALS OF NEUROLOLOGY
2006 Mar;59(3):499-503.

HEADACHE: links with epilepsy

This study looked at clinical evidence for a link between migraine and epilepsy in children and adolescents. Its impetus was the hypothesis of a shared mechanism due to underlying cortical hyperexcitability. In 137 children and adolescents seen consecutively in an Italian clinic with tension-type and migraine headaches, 14 (10.2%) had a positive history of febrile seizures, isolated seizures or epilepsy. The strongest association was with migraine with aura. 'Specific' electroencephalographic abnormalities were seen in 11.7% of the patients. In those with migraine with aura, ten of 23 (43%) had interictal EEG abnormalities. The authors suggest that these findings support the hypothesis of a possible clinical continuum between some types of migraine with aura and epileptic seizures. They propose that these conditions share an underlying pathophysiology, with resultant hyperexcitability. Ongoing research in the genetics of epilepsy and migraine, and particularly channelopathies, is providing details of potential mechanisms for this link. Despite potentially shared underlying mechanisms, the clinical implications of the two diagnoses, or having both diagnoses, are very different. The correct diagnosis or diagnoses relies on integrating the clinical findings and investigations. In this study, the significant incidence of EEG changes in the patients with migraine is important, as these could result in an erroneous label of epilepsy. These findings highlight the potential difficulty of distinguishing the conditions, particularly migraine with visual aura and occipital epilepsies. Given the established rate of misdiagnosis of epilepsy in both children and adults, it also demonstrates that investigations, in this case the EEG, have to be interpreted with great caution. - ***HAL***

Piccinelli P, Borgatti R, Nicoli F, Calcagno P, Bassi MT, Quadrelli M, Rossi G, Lanzi G, Balottin U.
Relationship between migraine and epilepsy in pediatric age.
HEADACHE
2006;46:413-21.

MULTIPLE SCLEROSIS: dodgy dendritic cells

Just when I thought I had worked out the immunology of multiple sclerosis, it all gets turned upside down again. Forget the T lymphocyte! The real culprit is the dendritic cell, so Krzysztof Selmaj would have you believe. The job of dendritic cells is to recognise an infection is happening and to present antigen to T cells. To get enough dendritic cells to experiment on, this collaboration between Lodz and Wurzburg had to subject 35 multiple sclerosis patients and 30 controls to a formal leucapheresis procedure. Then the peripheral blood mononuclear cell cultures were exposed to rounds of IL-3 and CD40L stimulation, which would normally 'mature' dendritic cells; but in the multiple sclerosis patients, this maturation was impaired. The functional effect of this was seen when dendritic cells were added to peripheral blood mononuclear cell cultures. The key finding, though, was that dendritic cells from multiple sclerosis patients completely failed to promote the regulatory (FoxP3+) T cell. So, the story now is that multiple sclerosis is due to hopeless dendritic cells failing to promote the generation of regulatory T cells and so allowing pre-existing enthusiastic anti-myelin T cells to rip up myelin unchecked. All very well. But (as in what came before the Big Bang?) this study just pushes us one level back: why do the dendritic cells fail in multiple sclerosis? - ***AJC***

Stasiolek M, Bayas A, Kruse N, Wieczarkowiecz A, Toyka KV, Gold R, Selmaj K.
Impaired maturation and altered regulatory function of plasmacytoid dendritic cells in multiple sclerosis.
BRAIN
2006;129:1293-305.

World Parkinson Congress

Washington DC, USA, 22-26 February, 2006.

The first ever World Parkinson Congress gathered together over 3000 people in Washington in late February. The group attending consisted of scientists, clinicians, other medical therapists, patients and carers. As such, the meeting was a true mix of those with the disease and those interested in it at both the scientific and medical level. The four day meeting began each day with two exemplary lectures giving way to a range of parallel sessions that were broadly divided into science and community based presentations, totalling about 16 in a day. This was then followed by final sessions on hot topics selected from the poster presentations and a wrap up from all those chairing the majority of the parallel sessions. It is thus impossible to do justice to the meeting, but a number of common themes emerged.

What is Parkinson's disease?

Fundamental to the whole four days was a growing frustration with our inability to define Parkinson's disease (PD). The long held view that PD is a movement disorder with nigrostriatal dopaminergic loss is not in doubt but the recent pathological staging by Braak et al has highlighted the extent to which pathology extends out of this pathway, and with this the growing realisation that clinical features are multiple and involve a large number of different domains. However, as many argued, if we are not to use the term Parkinson's disease because we don't know what it is, with what should it be replaced? Alternatives included the Parkinson's complex, Parkinsonian syndrome, the shaking palsy and Parkinson-Lewy disease. In addition there was a consensus that seemed to be emerging that the term Parkinson's disease or equivalent should only refer to conditions where there is no known aetiology, in which case the genetic causes of "PD" would lie outside the definition, which may help in clarifying an important distinction at this stage between genetic parkinsonism and sporadic Parkinson's disease.

The genetics of Parkinson's disease

The genetics of Parkinson's disease continues to be a major research issue and during this meeting several issues emerged on a number of occasions. Firstly, the recent identification of families with duplication or triplication of alpha synuclein resulting in Parkinson's disease with dementia clearly shows that this protein expressed at high levels but in a normal form can induce widespread pathology, highlighting that protein load as much as abnormalities in protein structure and function can cause disease. In addition the recent interest in the LRRK2 gene as a relatively common cause of Parkinson's disease continues to gain consensus, with estimates of about 5% in familial cases and 1.5% in series of sporadic cases. However, there is clearly a great deal of variability depending on ethnic groups, with a particular emphasis in North Africans and Ashkenazi Jews. Finally, heterozygosity in autosomal recessive forms of Parkinson's disease continues to be a very active issue, in particular the extent to which carrying one single abnormal gene predisposes people to developing the disease. It appears that in some cases this is true but the extent to which this happens requires further clarification.

Dr Stanley Fahn, Chair of the World Parkinson Congress (WPC), welcomed the attendees and gave a brief history of the WPC.

Mary Baker, President of the European Parkinson's Disease Association introduced the Global Declaration on PD which was launched in December 2003 in Mumbai, India.

Michael J Fox, actor and PD advocate, welcomed the attendees at the first-ever World Parkinson Congress in February 2006 in Washington DC, USA. He thanked the medical professionals who dedicated their lives to curing PD or improving the care and he thanked the patients and caregivers who took an active role in fighting PD.

Is there a pre- Parkinson's disease state?

There was much discussion about detecting the presymptomatic phase of PD with several studies suggesting that this may be recognised as a state of constipation, REM sleep behavioural disorder and a loss of olfactory function. However, if you believe that such a state exists then questions arise as to the 'at-risk' group which should be screened, especially given that we don't have any effective neuroprotective treatments. Thus should we be screening relatives of patients with Parkinson's disease, elderly patients, or whole populations? Indeed such questions as this also arise in the genetic screening of patients, given the issues raised above.

The non-motor features of Parkinson's disease

The non-motor features of Parkinson's disease continue to generate a great deal of interest. There is now a growing realisation that cognitive deficits are common in Parkinson's disease and that ultimately 30% of patients will develop a dementia with this condition. Identifying this subgroup of patients is a key issue and the risk factors that seem important and are emerging are increasing age of patient and disease duration, non tremor akinetic rigid forms of the disease and early hallucinations with behavioural abnormalities. The cause of this aspect of PD seems to be at the neurochemical level related to cholinergic deficits, whilst the pathological correlate appears to be Lewy body formation in the cortex. In terms of other non-motor features, the affective aspects of PD also seem common, with about 40% of patients having depression at some point in their disease course, although the aetiology and the optimal treatment of this remains controversial. Abnormalities of olfaction occur early in Parkinson's disease, as mentioned before, but it does not seem to necessarily progress over time, so whilst helping possibly in the diagnosis it may not be a good longitudinal biomarker - similar to the story with the REM behavioural sleep disorder in PD.

The pathogenesis of Parkinson's disease

The pathogenesis of Parkinson's disease was discussed in the context of two particular models. The first model of disease uses known genetic abnormalities in transgenic animals, whilst the second uses established neurotoxin models. The former model using transgenic animals informed us once more on the role of protein aggregation and how this may lead to cell death, possibly through mitochondrial and proteosomal dysfunction. In the second approach using neurotoxic models there was a great deal of interest in the extent to which inflammation may be driving disease progression. I think it is fair to say that this remains controversial and unproven.

Other issues

Other issues that surfaced a number of times during the meeting were biomarkers, especially those relying on functional imaging and systems approaches. Many of these new techniques use complex statistical analysis, especially principal component analysis, a process where one identifies a series of abnormalities in patients with Parkinson's disease that forms a distinctive signature that can then be used to distinguish it from other conditions. At the moment these techniques remain in their infancy but nevertheless offer enormous potential and there were particularly powerful demonstrations of this using metabolic PET imaging and lymphocyte proteomic profiling.

Novel treatment approaches were also discussed although surprisingly little was mentioned on GDNF and stem cells, at least within the sessions that I attended. There seemed to be more on viral gene therapies which are entering, or are about to enter, the clinic, including the AAV GAD delivery to the subthalamic nucleus and the planned neurturin growth factor study.

Dr Oliver Sacks, Honorary Chair of the Creativity & PD Subcommittee, greeted the audience and encouraged them to actively participate in the creative side of the WPC and to remember to keep a sense of humour.

Finally, there were sessions on a mass of other issues that affect patients with PD, including the value of alternative non-drug therapies such as music therapies, language therapy, as well as a great deal of time given to the importance of developing more effective inter-disciplinary teams to help patients, carers and families with Parkinson's disease.

In conclusion, this meeting was a great success and a tribute to Stan Fahn, Howard Federoff and Elias Zerhouni who originally had the idea to put this event together. Of course with any new event of this scale there are teething problems and so there were issues of repetition, the number of parallel sessions and the absence of major gaps in the daily programme. Nevertheless, by virtue of being a one disease meeting and involving everyone involved with PD, including patients, it meant that many useful discussions and themes were developed which helped focus attention onto the key issues, and as such help set up the critical questions which will no doubt form the basis of the second World Parkinson Congress planned for Paris in 2009.

Roger A Barker,
Honorary Consultant in Neurology,
The Cambridge Centre
for Brain Repair.

4th World Congress for Neurorehabilitation

Hong Kong, China, 13-16 February, 2006.

Hong Kong, although now technically part of China, likes to market itself as the gateway to China where 'East meets West'. Although there was no formal theme to the conference (which was mentioned by a few delegates) the prevailing theme was very much 'East meets West' of Neurorehabilitation.

The congress got off to a good start with the opening ceremony thankfully short on speeches, followed by a wonderful performance of four two-person (traditional Chinese) costumed dragons who jumped between pedestals around the stage to the beat of Oriental drums. There were nearly 1500 delegates from all disciplines and all six continents represented, the Asians naturally being the most numerous. The programme included a wide variety of topics (from botulinum toxin to tai chi) covered in the plenary, parallel and free paper sessions with generous coffee/tea breaks and lunch of an hour and a half to allow for discussion, or a quick spot of shopping.

With the parallel sessions one was often in a dilemma to choose between some very promising talks on at the same time. As expected, this report reflects my own interests and attendance rather than a pick of the best talks.

The opening session on "Neuroplasticity and Recovery of Brain Function" was a look to the future of the science underlying rehabilitation, featuring two speakers from the US. The first speaker from the NIH outlined how recent studies using fMRI, PET, TMS and MEG demonstrated interhemispheric interactions as influential in motor recovery after stroke. Increased somatosensory feedback from the paretic and reduction from the intact arm (possibly the mechanism of constraint therapy) as well as pharmacological interventions have potential to improve motor performance of the paretic arm. The second talk was on the migration of neuroblasts from the subventricular zone to the peri-infarct cortex in the mouse model. So the adult mammal brain does have some potential for neuroregeneration after all. As the area around the infarct ('peri-infarct niche') exists in an area of altered blood-brain barrier the potential for systemic drugs to improve neural repair apparently beckons.

There was an excellent presentation by Prof. Delph from Stanford on the development of a computer model to simulate the biomechanical factors of human gait. He illustrated graphically with this model how altered postures can change the 'usual' action of a muscle and thus will impact on choice of target muscle for treatment. His models are subject-specific and thus allow for prediction of effect of interventions such as botulinum toxin in an individual. One hopes that the 2-3 years he predicts for a widely available and reasonably priced product on the market will be realised.

In other plenary sessions, there were two talks on robotics and the developments in this area of rehabilitation, although one of these had a bit too much technical emphasis. The last plenary session covered the role of genetics in recovery after brain injury and their potential roles in practice. The group from the University of Southampton presented data on apolipoprotein E gene association with poorer outcome in traumatic brain injury and other conditions. Future work may allow better prediction of individual outcome and also to identify targets for therapy.

There were interesting sessions on cognitive rehabilitation after traumatic brain injury and the use of new technology, especially internet-based telerehabilitation. The group from Hong Kong Polytechnic University paid a touching tribute to one of their colleagues, Professor Alan Tam (who died unexpectedly last year) and presented work he was involved with in "telestroke and telerehabilitation". Two centres from Italy also presented some of their work and research to allow more rehabilitation to occur in the home setting.

Mild Traumatic Brain Injury affects large numbers of individuals each year (100-300/100,000 population). Although no new findings were presented, the questions and answers did clarify some issues over the continuing lack of definition and that simple written information seems as effective as more complex intervention for routine follow-up.

Speaking to attendees, it was clear that the challenges faced by all countries were similar: competition for limited healthcare funding, continued need to demonstrate evidence for rehabilitation and innovations with new technologies and techniques. The congress provided an overview of current knowledge, with a look at what the future may hold, but also an opportunity to share and discuss ideas and experiences.

One of the best features of the conference was the 'technical visit' to a number of rehabilitation centres in Hong Kong. I was in the group to visit Kowloon rehabilitation and spinal unit. It was fascinating to see how they were so advanced technologically, yet staffing ratios, especially in nursing, raised a few eyebrows amongst the visitors. Not surprisingly, there was close integration of traditional and Western medicine.

Whatever the extra-curricular attractions of Hong Kong, the next congress in 2008 to be held in Rio de Janeiro had more than a few making plans to present their next research project there.

John Macfarlane,
Consultant in Rehabilitation Medicine,
Hunters Moor Regional Neurorehabilitation
Centre, Newcastle.

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To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by May 31st, 2006

2006

May

4th International Symposium on Neuroprotection and Neurorepair: Cerebral Ischemia and Stroke
3-6 May, 2006; Magdeburg, Germany
W. www.neurorepair-2006.de/nr/

European Regional Meeting of the International Psychogeriatric Association
3-6 May, 2006; Lisbon, Portugal
W. www.ipa-online.org/ipaonlinev3/meetings/meetingannouncements/...
E. 2006lisbon@ipa-online.org

NEW
BISWG South Wales and the West Country Regional Meeting
4 May, 2006; Cardiff, UK
Info. Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

RSM Neurological Disorders in Pregnancy
4 May, 2006; London, UK
Info. Laura Matthews
T. +44 (0)20 7290 3848
E. sponsorship@rsm.ac.uk

Jahrestagung der Deutschen Gesellschaft für Epileptologie
4-6 May, 2006; Strasbourg, France
W. www.dgfe.info

Cochrane Systematic Reviews in Practice: Parkinson's Disease
5-6 May, 2006; Lisbon, Portugal
E. cochrane.neuronet@unimi.it

NEW
Talk: Personalised Medicines
9 May, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

1st Mediterranean Epilepsy Congress
10-14 May, 2006; Sharm El Sheikh, Egypt
W. www.epilepsysharm2006.com/

Primary Care Neurology 2006
11 May, 2006; London, UK
P-CNS website. www.p-cns.org.uk

NCYPE Managing Epilepsy
11 May 2006, Lingfield, Surrey, UK
Info. Ruth Norman
T. 01342 832 243
W. www.ncype.org.uk

NEW
MS Trust General Study Days
16 May, 2006; Ayrshire, UK
T. 01462 476704
W. www.mstrust.org.uk/education.jsp

BISWG Annual General Meeting and Case Discussions
16 May, 2006; Birmingham, UK
Info. Guy Soulsby
T. 0151 250 6247
E. guy.soulsby@merseycare.nhs.uk

15th European Congress of Physical and Rehabilitation Medicine
16-20 May, 2006; Madrid, Spain
Info. Congress Office,
Diputación 401 Bajo O8013, Barcelona
T. +34 93 2463566
F. +34 93 2317972

NEW
Talk: Creativity and the Mind
17 May, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

Targeting Adenosine A2A Receptors in Parkinson's Disease. Boston
17-19 May, 2006; MA, USA
Info. Galina Slezinger, Mass General Institute for Neurodegenerative Disease
T. +1 617-724-9611
E. michaels@helix.mgh.harvard.edu
W. www.A2APD.org

NEW
Talk: Brain Surgery
18 May, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

NEW
Spine 2006: State of the Art in Spinal Disorders
18-20 May, 2006; Sorrento (NA), Italy
W. www.csrcongressi.com
E. info@csrcongressi.com
T. +39 051 765357
F. +39 051 765195

NEW
OPINIONS IN.....PD
A series of meetings to explore the statement: "There's more to Parkinson's disease than motor symptoms"
23 May, 2006; Brighton, UK
20 June, 2006; Peterborough, UK
27 June, 2006; Bristol, UK
E. info@onyxhealth.com

NEW
Talk: Pain
24 May, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

3rd Joint National Brain Injury Conference (Brain Injury – The Quality Agenda)
24 - 25 May, 2006; York, UK
E. fwinder@partnershipsincare.co.uk or Kemsley@standrew.co.uk
W. www.qualityagenda.co.uk

16th Meeting of the European Neurological Society
27-31 May, 2006; Lausanne, Switzerland
W. www.akm.ch/ens2006/

International conference on Monitoring sleep and sleepiness - from physiology to new sensors
29-30 May, 2006; Basel, Switzerland
E. enquiries@sleeping.org.uk

NEW
Talk: Synaesthesia
31 May, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

6th Congress of the Federation of European Psycophysiology Societies
31 May-3 June, 2006; Budapest, Hungary
W. www.feps2006.com

Consortium of Multiple Sclerosis Centers (CMSC)
31 May – 4 June, 2006; Phoenix, USA
E. info@mscare.org

June

8th Annual Neurology SpR Study Weekend June 2006
E. lucie@medivents.co.uk

RSM HIV-AIDS Neurology
1 June, 2006; London, UK
Info. Laura Matthews
T. +44 (0)20 7290 3848
E. sponsorship@rsm.ac.uk

NEW
BISWG Dumfries, Scotland -Study Day
2 June, 2006; Dumfries, Scotland
Info. Fen Parry
T. 0131 537 6853
E. fen.parry@edinburgh.gov.uk

NEW
28th Advanced Clinical Neurology Course
5-7 June, 2006; Edinburgh, Scotland
Info. Judi Clarke, Western General Hospital
T. 0131 537 2082
F. 0131 332 5150
E. judi.clarke@ed.ac.uk
W. www.dcn.ed.ac.uk

NEW
MS Trust General Study Days
6 June, 2006; East Sussex, UK
T. 01462 476704
W. www.mstrust.org.uk/education.jsp

Advances in the Diagnosis and Management of Early-Stage Parkinson's Disease
6–22 June, 2006; a series of UK meetings
6 June, 2006; Manchester, UK
8 June, 2006; Edinburgh, UK
14 June, 2006; London, UK
15 June, 2006; Bristol, UK
22 June, 2006; Birmingham, UK
T. 020 8326 3135
E. events@chameleon-uk.com

10th International Child Neurology Congress
11-16 June, 2006; Montreal, Canada
W. www.icnc2006.com
E. info@eventsintl.com

5th International Congress on Mental Dysfunction in Parkinson's Disease
12-14 June, 2006; Amsterdam, The Netherlands
Info. J Desel-Willems, SCEM Conference Services
T. +1 31-345-57-66-42,
F. 1-31-345-57-17-81;
E. scem@scem.nl
W. www.mdpdamsterdam.nl

European Pain School 2006. Pain and Central Nervous System
12-18 June, 2006; Siena, Italy
Info. Prof. Anna Maria Aloisi
T. +39 0577234103
F. +39 0577234037
E. uropeanpainschool@unisi.it
W. www.unisi.it/pain-school/

41st Annual Scientific Meeting of the Canadian Congress of Neurological Sciences
13-17 June, 2006; Montreal, Quebec, Canada
Info. CCNS Secretariat Office by
E. brains@ccns.org
W. www.ccns.org
T. 1+(403) 229-9544
F. 1+(403) 229-1661

NEW
Talk: Creativity in Ageing
14 June, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

NEW
BISWG West Midlands Regional Meeting
19 June, 2006; Stourbridge, West Midlands
Info. Lucy Devlin
T. 01384 244654
E. lucy.devlin@dgoh.nhs.uk

6th International Congress of Neuroendocrinology
19-22 June, 2006; Pittsburgh, USA
T. 001 412 6478232
E. CCEHS@upmc.edu
W. www.upmc.edu/CCEHS/cme/formal_courses.asp

International Communication Association
19-23 June, 2006; Dresden, Germany
W. www.icahdq.org

NEW
Public consultation into Ageing
22 June, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

RCN Neuroscience Nursing Forum conference Neuroscience nursing: moving ahead 2006
24 June, 2006; London, UK
E. pat.anslow@rcn.org.uk

Cognitive Rehabilitation for Physiotherapists, following brain injury
24 June, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

Updates in Neuro-Oncology
24-26 June, 2005; Arezzo, Italy
E. ctartaglia@csrcongressi.com
W. www.csrcongressi.com

Neurotology Symposium
25-30 June, 2006; Antalya, Turkey
F. 02 123 610 507
T. 02 123 610 504

RSM Medicine and Me: Dementia - the early stages
26 June, 2006; Cardiff, UK
Info. Simon Timmis
T. 0207 290 3844
E. simon.timmis@rsm.ac.uk

9th International Conference on Cerebral Vasospasm
27-30 June, 2006; Istanbul, Turkey
T. +90 212 292 8808
E. info@interium.com.tr
W. www.cerebralvasospasm9.org

ISVR Balance Advanced Course
26-28 June, 2006; Southampton, UK
Info. Lyndsay Oliver
T. 023 8059 2287
E. lo@isvr.soton.ac.uk

The fMRI Experience
27-30 June, 2006; Melbourne, Australia
W. http://fmriexp.com/8/index.htm

NEW
Talk: Brain Imaging
28 June, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

ISSCR meetings (International Society for Stem Cell Research)
29 June – 1 July, 2006; Toronto, Canada.
Info. International Society for Stem Cell Research
T. +847-509-1944
F. +847-480-9282
E. isscr@isscr.org

July

7th European Congress on Epileptology
2-6 July, 2006, Helsinki, Finland
W. www.epilepsyhelsinki2006.org/

International Congress on Neuromuscular Disorders 2006 (ICNMD)
2-8 July, 2006; Istanbul, Turkey
W. www.icnmd2006istanbul.org
E. pirayes@hotmail.com

NEW
Talk: Pain, drugs and plants
4 July, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

Towards an understanding of Parkinson's disease
4 July, 2006; Devon, UK
T. 01392 405171

NEW
11th Wye College Advanced Neurosciences Symposium
5-7 July 2006, Wye, Kent, UK
W. www.bns.org.uk

NEW
BSRM/SRR Summer Meeting
5-7 July, 2006; London, UK
Info. BSRM
T. 01992 638865,
E. admin@bsrm.co.uk,
W. www.bsrm.co.uk

5th Forum of European Neuroscience
8-12 July, 2006; Vienna, Austria
W. http://forum.fens.org/2006

NEW
MS Trust Advanced Study Day
10 July, 2006; Liverpool, UK
T. 01462 476704
W. www.mstrust.org.uk/education.jsp

Multidisciplinary care in Parkinson's disease and parkinsonism from science to practice - the 11th National Conference
11 July, 2006; London, UK
W. www.mepltd.co.uk/conference_pd_2006.html
E. alockyer@mepltd.co.uk

13th International Meeting on Advanced Spine Techniques (IMAST)
12-16 July, 2006; Athens, Greece
W. www.imastonline.org/

Launch of Neupro® — the first dopamine agonist patch — provides new approach to treatment of Parkinson's disease

Patients with early-stage Parkinson's disease could benefit from an innovative treatment launched in the UK on 5 April 2006. Neupro® (rotigotine transdermal patch), developed by Schwarz Pharma, combines a new dopamine agonist, rotigotine, with the benefits of a transdermal delivery system.

The transdermal delivery system of Neupro® provides consistent and continuous drug delivery over 24 hours and proven efficacy in early Parkinson's disease. The patient needs to wear a patch, which is applied once a day. Drug delivery via a transdermal patch eliminates the peaks and troughs in drug levels associated with oral treatment that can lead to fluctuations in symptom control. Once-a-day dosing is likely to be more convenient for patients than taking tablets several times a day.

Daily activities, such as shaving, can continue as normal when wearing the Neupro® patch.

The new dopamine agonist, rotigotine – the active ingredient in Neupro® – has a receptor-binding profile that is very similar to naturally occurring dopamine, and is a new and innovative treatment option for early-stage Parkinson's disease.

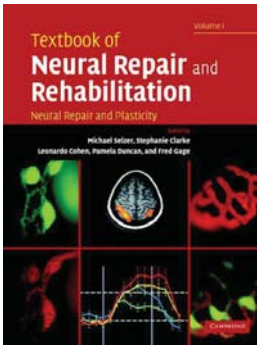
For more information see www.schwarzpharma.co.uk

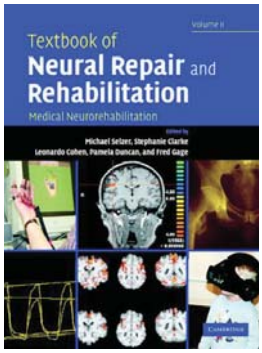
Abilify® (Aripiprazole) has superior effectiveness and improved metabolic profile compared to other standard-of-care antipsychotics

New data from the STAR (Schizophrenia Trial of Aripiprazole) study show that Abilify® (aripiprazole) demonstrated superior effectiveness to Standard-Of-Care (SOC; olanzapine, quetiapine, risperidone), as measured by the Investigator Assessment Questionnaire (IAQ) total score, which is based on 10 different factors. In this study, people with schizophrenia treated with aripiprazole experienced significantly less weight gain, and improved lipid profiles, sexual function and overall quality of life (QoL) compared to those treated with SOC antipsychotics. Overall, significantly more patients in the aripiprazole group than the SOC group whose symptoms were not controlled by their previous antipsychotic or who experienced tolerability issues, reported that aripiprazole was "much better" than their prior medication.

For further information contact aviva.kessler@popewoodhead.com

Textbook of Neural Repair and Rehabilitation





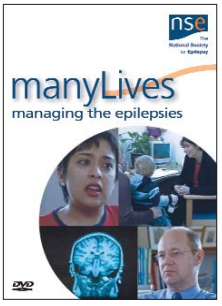
In two freestanding but linked volumes, Textbook of Neural Repair and Rehabilitation provides comprehensive coverage of the science and practice of neurological rehabilitation. Volume One, Neural Repair and Plasticity, covers the basic sciences relevant to recovery of function following injury to the nervous system, reviewing plasticity in the normal CNS, mechanisms of neuronal death, axonal regeneration, stem cell biology and current research strategies. Volume Two, Medical Neurorehabilitation, provides authoritative guidelines on the management of disabling symptoms and describes comprehensive rehabilitation approaches for the major categories of disabling neurological disorders. Edited and written by leading international authorities from the neurosciences and clinical neurorehabilitation, the two-volume set is an essential resource for rehabilitation professionals and a comprehensive reference for all scientists and clinicians in the field.

Textbook of Neural Repair and Rehabilitation:
978 0 521 85641 6, Volume 1: Neural Repair and Plasticity - £110.00
978 0 521 85642 3, Volume 2: Medical Neurorehabilitation - £110.00
978 0 521 83639 5, 2 volume set - £180.00 Save £60.00!

For further information contact Cherrill Richardson, Cambridge University Press, Email. crichardson@cambridge.org

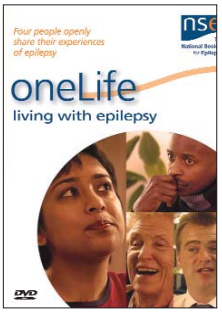
New Epilepsy DVDs from the National Society for Epilepsy

The NSE is producing two new DVDs:



manyLives: a 3-disc DVD educational programme for professionals involved in the treatment and management of epilepsy. It costs £120 including p&p and includes:

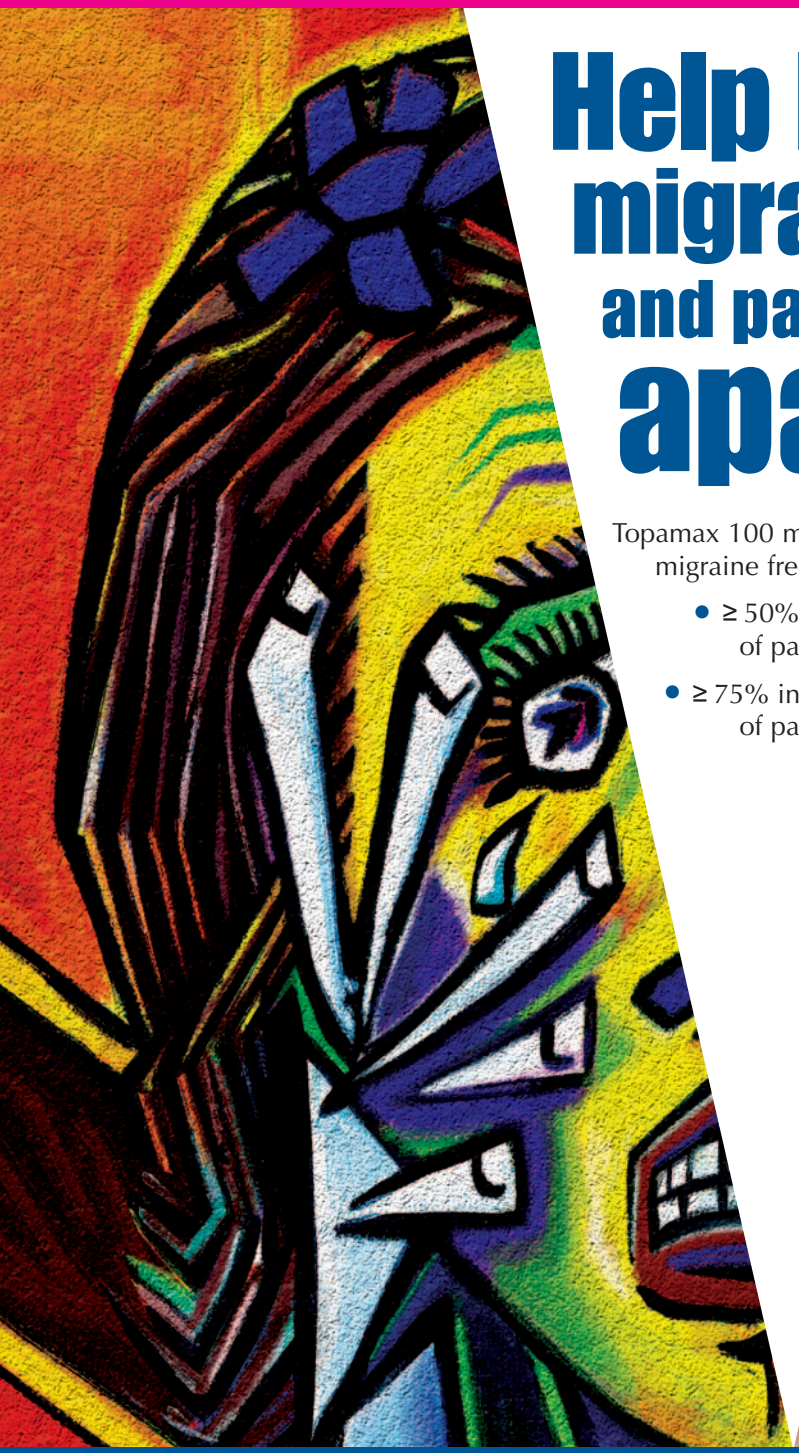
- An introduction to managing the epilepsies presented by Prof John Duncan
- 45 minute programme on the general principles of managing epilepsy
- oneLife - living with epilepsy: a 40 minute feature for people with epilepsy
- Printable tools including templates for referral letters and epilepsy audit tools
- Interviews with leading professionals on specific areas of care within epilepsy, including: women with epilepsy, epilepsy in later life, epilepsy in childhood and epilepsy and learning disabilities.



oneLife: for anyone who has been affected by epilepsy. It features four adults talking about how epilepsy has affected their lives and what having epilepsy means to them. It will be available to buy in either DVD or VHS format, for £12, including p&p.

For more information contact Amanda Cleaver, National Society for Epilepsy, Tel. 01494 601404 (direct line), Email. amanda.cleaver@epilepsynse.org.uk

NOW LICENSED AS A NEW SPECIALIST OPTION IN MIGRAINE PROPHYLAXIS



Help keep migraines and patients apart

Topamax 100 mg/day reduced migraine frequency by:

- ≥ 50% in 46% of patients[1]
- ≥ 75% in over 25% of patients[1]

TOPAMAX® (topiramate)

Every migraine-free day is a good day

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses: Epilepsy**: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. **Migraine prophylaxis** when 3 or more attacks/month; attacks significantly interfere with daily routine. Six monthly review. Use in acute treatment not studied. Initiation: specialist care. Treatment: specialist supervision/shared care. **Dosage and Administration**: Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. **Epilepsy**: Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3-6 mg/kg/day (two divided doses). Initiate at 0.5-1 mg/kg nightly with weekly or fortnightly increments of 0.5–1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5-9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1-3 mg/kg. **Migraine**: Over 16 years: Usually 100 mg/day (in two divided doses). Initiate at 25 mg nightly with weekly increments of 25 mg. Longer intervals can be used between dose adjustments. Children under 16 years: Not studied. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. **Contra-indications**: Hypersensitivity to any component. **Precautions and Warnings**: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Depression/mood alterations have been reported. Monitor for signs of depression; refer for treatment, if appropriate. Suicidal thoughts: Patients/caregivers to seek immediate medical advice. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and require discontinuation of Topamax and treatment. Increased risk of renal stones. Adequate hydration is very important. Bicarbonate level may be decreased so monitor patients with conditions/drugs that predispose to metabolic acidosis and reduce dose/discontinue Topamax if acidosis persists. Galactose intolerant, Lapp lactase deficiency, glucose-galactose malabsorption: do not take. **Migraine**: Reduce dose gradually over at least 2 weeks before discontinuation to minimise rebound headaches. Significant weight loss may occur during long-term treatment. Regularly weigh and monitor for continuing weight loss. Food supplement may be required. **Interactions**: Possible with phenytoin, carbamazepine, digoxin, hydrochlorothiazide, pioglitazone, oral contraceptives, haloperidol and metformin. Caution with alcohol/CNS depressants. **Pregnancy**: If benefits outweigh risks. Discuss possible effects/risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). **Lactation**: Avoid. **Side Effects**: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis reported rarely. Suicidal ideation or attempts reported uncommonly. Bullous skin and mucosal reactions reported very rarely. **Pharmaceutical Precautions:** Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. **Legal Category:** POM **Package Quantities and Prices**: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.92, 50 mg (PL0242/0302) = £34.36; 100 mg (PL0242/0303) = £61.56; 200 mg (PL0242/0304) = £119.54. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.04, 25 mg (PL0242/0349) = £24.05, 50 mg (PL0242/0350) = £39.52 **Product licence holder**: JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ. UK. **Date of text revision**: August 2005. **APIVER150805**.

Reference: 1. Bussone G, Diener H-C, Pfeil J *et al.* Topiramate 100mg/day in migraine prevention: a pooled analysis of double blind randomized controlled trials. Int J Clin Pract 2005; 59(8): 961-968.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Janssen-Cilag Ltd.

JANSSEN-CILAG Ltd

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