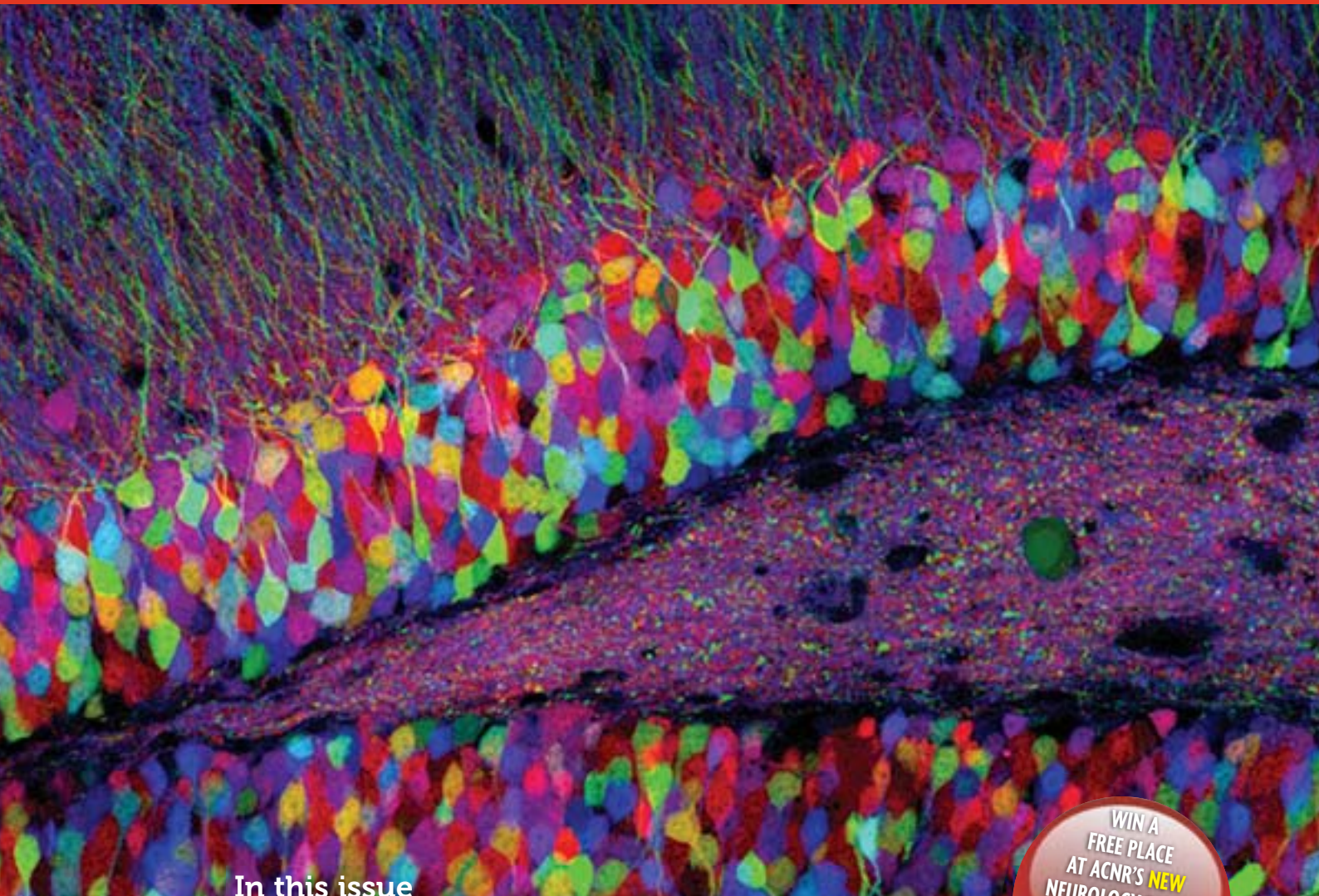


ACNR

www.acnr.co.uk

ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

J Helen Cross

The Ketogenic Diet

Anette Storstein and Christian Vedeler

Treatment of Paraneoplastic Neurological Syndromes

Terry Pratchett

Living with Dementia

WIN A
FREE PLACE
AT ACNR'S **NEW**
NEUROLOGY DIGEST
MEETING
SEE PAGE 4 FOR
MORE DETAILS

INSIDE > FREE ACNR 2009 wallplanner

Simplicity *in a complex disease*


Once-Daily
AZILECT[®]
rasagiline
Simplicity

Azilect[®] 1mg tablets Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food. **Elderly:** No change in dosage required. **Children and adolescents (<18 years):** Not recommended. **Patients with renal impairment:** No change in dosage required. **Patients with hepatic impairment:** Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic insufficiency. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, MAO inhibitors and a selective MAO-B inhibitor. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use

in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. **Undesirable effects in clinical trials: Monotherapy:** >1%: headache, flu syndrome, malaise, neck pain, dyspepsia, arthralgia, depression, conjunctivitis, allergic reaction, fever, angina pectoris, anorexia, leucopenia, arthritis, vertigo, rhinitis, contact dermatitis, vesiculobullous rash, skin carcinoma, hallucinations, urinary urgency. <1%: cerebrovascular accident, myocardial infarct. **Adjunct therapy:** >1%: abdominal pain, accidental injury, postural hypotension, constipation, vomiting, weight loss, dyskinesia, neck pain, anorexia, dry mouth, arthralgia, tenosynovitis, dystonia, abnormal dreams, ataxia, rash, hallucinations. <1%: angina pectoris, cerebrovascular accident, skin melanoma, confusion. Please refer to the SmPC for a full list of adverse events. **Basic NHS Price:** Azilect[®] (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** May 2008 **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.



New Hope of Dignity for People with Stroke

The University of Central Lancashire (UCLan) has received a £1.2 million grant awarded by the Department of Health (National Institute for Health Research) to research new ways of assessing and managing urinary incontinence after stroke. The project, ICONS: Identifying Continence Options after Stroke, will develop and test a package of care designed to increase the number of stroke survivors with urinary incontinence who become continent again.

The research, headed by Professor Caroline Watkins and Dr Lois Thomas at UCLan, is a collaborative project between Lancashire Teaching Hospitals NHS Foundation Trust, Wirral University Hospital NHS Foundation Trust, the Clinical Practice Research Unit at the University of Central Lancashire, and the Universities of Bangor, Edge Hill, Glasgow, Glasgow Caledonian, Leeds and Newcastle upon Tyne.



Professor Caroline Watkins



Dr Lois Thomas

Professor Caroline Watkins at UCLan commented: "We are delighted to have been awarded this funding as we are about to embark on a significant piece of research that will provide valuable insights into how best to care for incontinent stroke patients. Ultimately, this could improve such stroke patients' lives significantly, most importantly because it could restore their dignity. There has been little high quality research into nursing topics after stroke; this flagship project into a key topic for nursing may prompt further robust research to increase the evidence base of nursing interventions with patients after stroke." The programme will involve 13 stroke services and around 850 patients in total, with the potential for further roll out across 30 stroke services.

For further information contact:
E. mmansfeld@webershandwick.com
T. 020 7067 0464

The Professor Mary Robertson Prizes 2009

Professor Mary Robertson and Tourettes Action invite entries for a new annual essay prize for medical students and for medical trainees (in any speciality or grade) on any aspect of the Gilles de la Tourette syndrome.

Entries do not need to contain original data. Closing date: February 28, 2009. Award of Prizes: March 28, 2009.

For details please see
<http://tourettes-action.squarespace.com/prof-mary-robertson-prizes/>



Honours for Institute Staff

Professor Geraint Rees (Institute of Cognitive Neuroscience, Wellcome Trust Centre for Neuroimaging) was recently awarded the 2009 Goulstonian Lecture, which he will deliver at the Royal College of Physicians of London on 26th February 2009. He will discuss recent advances in brain imaging technology that show it is possible to accurately decode changes in an individual's conscious awareness based only on non-invasive measurements of their brain activity. These 'brain reading' abilities may transform



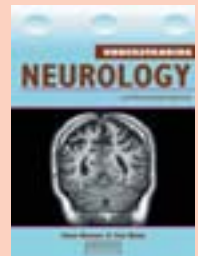
Professor Geraint Rees

our understanding of the brain, and provide important new medical insights; but they also raise important ethical issues concerning the privacy of personal thought. Rees will describe recent work in this area, while setting it in the broader context of medical diagnosis and treatment.

For more information see
www.ion.ucl.ac.uk

Understanding Neurology Competition Winners

Congratulations to Saleem Khan and Sarah Pashley who entered our competition in the last issue of ACNR. They win copies of *Understanding Neurology* by John Green and Ian Bone, courtesy of Manson Publishing.



Carl Zeiss Wins Thuringian Innovation Award for Fourth Time



Carl Zeiss has been awarded the 2008 Thuringian Innovation Award for the LSM 710 Laser Scanning Microscope. This is the fourth time in the eleven years that the Competition has been running that Carl Zeiss has been selected to receive the Innovation Award, which is presented to highlight the significance of future-oriented innovations and design excellence for manufacturing companies

and research institutes. "Research conducted with multifluorescent-labelled living cells is of fundamental importance in the quest for a better understanding of the disease process," explains Aubrey Lambert, Carl Zeiss UK. All areas of biological research will benefit from the LSM 710's enhanced image quality, improved flexibility for experiments and new optical and technical details. Featuring outstanding sensitivity, the LSM 710 provides high-contrast, detailed images - even of complex specimens such as thick, living tissue samples.

For more information contact: micro@zeiss.co.uk

Greenfield's Neuropathology Prize Winner

Congratulations to Dr Zandi from Cambridge, who won a copy of *Greenfield's Neuropathology, Eighth Edition* in the prize draw in our Nov/Dec issue.



CONTENTS

JANUARY/FEBRUARY 2009

03 Awards & Appointments

06 From the Editor...

Review Articles

08 The Ketogenic Diet

J Helen Cross

12 Treatment of Paraneoplastic Neurological Syndromes

Anette Storstein, Christian Vedeler

15 Improving the Effectiveness of Drugs in Epilepsy through Concordance

Hermann Stefan

Rehabilitation Article

20 Young People with Cerebral Palsy in Transition from Paediatric to Adult Health Services

AMO Bakheit

Personal Experiences

22 Living With Dementia

Terry Pratchett

Neuropathology Article

24 Recent Advances in Glial Tumours

Kathreena Kurian

Neurological Literature

27 Headache: Part 5

Andrew Lerner

Regulars

29 Events Diary

31 Conference News

35 Journal Reviews

37 Book Reviews

38 News Review

ACNR

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

ADVERTISING

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

COURSE ADVERTISING

Nathalie Fricker E. events@acnr.co.uk

EDITORIAL

Anna Phelps E. editorial@acnr.co.uk

DESIGN & PRODUCTION DEPARTMENT

E. design.dept@sky.com

PRINTED BY

Warners Midlands PLC, T. 01778 391000

Copyright: All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without either the prior written permission of the publisher or a license permitting restricted photocopying issued in the UK by the Copyright Licensing Authority.

Disclaimer: The publisher, the authors and editors accept no responsibility for loss incurred by any person acting or refraining from action as a result of material in or omitted from this magazine. Any new methods and techniques described involving drug usage should be followed only in conjunction with drug manufacturers' own published literature. This is an independent publication - none of those contributing are in any way supported or remunerated by any of the companies advertising in it, unless otherwise clearly stated. Comments expressed in editorial are those of the author(s) and are not necessarily endorsed by the editor, editorial board or publisher. The editor's decision is final and no correspondence will be entered into.



Cover shows the picture which won 18th place in the Nikon Small World 2008 Competition: 'Brainbow' transgenic mouse hippocampus (40x), Confocal.

Picture by Dr Tamily Weissman, Harvard University, Cambridge, Massachusetts, United States.

Founded in 1974 to recognise excellence in photography through the microscope, Nikon Small World is the leading forum for celebrating the beauty and complexity of objects seen through the light microscope

Win

ACNR's Neurology Digest

26th March, 2009, Royal Society of Medicine, London

ACNR is delighted to introduce "Neurology Digest", a new series of half day events run in partnership with Innervate Ltd, the secretariat to the Primary Care Neurology Society.

Each event will focus on recently published key papers in neuroscience, neurology and therapeutics including rehabilitation, 'digest' the content of the papers, and offer expert opinion on the implications for clinical practice.

The first event will focus on multiple sclerosis and

movement disorders and will be led by Roger Barker and Alasdair Coles, co-editors of ACNR.

Cost: £95 inc VAT.

For more information contact:
Neil Bindemann, Innervate Ltd,
Email: neil@innervate.co.uk
Tel. 020 7921 0002



Win a free delegate place at ACNR's Neurology Digest Meeting

We are giving one reader the opportunity to attend ACNR's inaugural Neurology Digest meeting free of charge - normal delegate rate £95 inc VAT.

The meeting will take place at the Royal Society of Medicine in London, on the afternoon of March 26th 2009, and will focus on multiple sclerosis and movement disorders.

To enter, simply email your details to Rachael@acnr.co.uk

The winner will be the first name drawn after the closing date of February 13th.

As soon as first line oral
dopamine agonists start to fail
Go directly to **APO-go**

GO



Trying subsequent oral medication once your PD patient's first line dopamine agonist begins to fail, resulting in increasing motor complications, can be a time of frustration and disappointment for you and your patient – compromising their optimum quality of life.

For responsive patients with Early Complex PD, APO-go CDS is a highly effective,^{1,2} rapid-acting³ drug that, combined with Britannia's extensive Package of Care, can maintain your PD patients' independence.⁴


Prescribing information can be found overleaf.



 **Britannia**
Pharmaceuticals

Britannia Pharmaceuticals is a trading name of Genus Pharmaceuticals Ltd.

Version Number: APG.API.V9.

Confidence in
consistent control 
APO-go[®]
apomorphine hydrochloride

ABBREVIATED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL04483/0064. APO-go Pens: PL04483/0065. APO-go Pre filled syringes: PL05928/0025. **Legal Category:** POM. **Date of last revision:** October 2008. For further information please contact: Britannia Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

References: 1. Pietz K, Hagell P, Odin P, 1998. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *J Neurol Neurosurg Psychiatry*. 65:709-716. 2. Lees A, Turner K, 2002. Apomorphine for Parkinson's Disease. *Practical Neurology*, 2:280-287. 3. Deleu D, Hanssens Y, Northway M G, 2004. Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease. *Drugs Aging*, 21(11):687-709. 4. Ellis C, Lemmens G et al 1997. Use of Apomorphine in Parkinsonian Patients with Neuropsychiatric Complications to Oral Treatment. *Parkinsonism & Related Disorders*, 3(2):103-107.

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

We have two contrasting review articles in this issue of ACNR. The first concerns epilepsy, the second paraneoplastic syndromes. Using a ketogenic diet to treat epilepsy has always been controversial since it was first reported in 1921. Helen Cross in her review gives us a clear account on the efficacy of this treatment in children with refractory epilepsy, albeit in studies that are largely open label in nature. Nevertheless, the data is persuasive and raises questions about the extent to which dietary manipulation in adults with epilepsy may be useful. The treatment of paraneoplastic neurological syndromes is often very disappointing. The need to identify the primary malignancy is clearly paramount but often therapies used to treat the neurological problem itself, are ineffective. Anette Storstein and Christian Vedeler from Bergen, Norway review this area and conclude that immunotherapies for these type of disorders do work occasionally, especially if the problem lies outside the CNS and in the periphery and in particular at the neuromuscular junction.



"A survey undertaken by Neurologists (n=661) in the USA revealed that 71% of patients with epilepsy forgot to take their AED (anti-epileptic drug) at least once per month and it was evident that the chance of a patient missing a dose increased with the number of tablets prescribed. Of patients that missed a dose, 45% reported a seizure." So writes Professor Hermann Stefan (a member of our international editorial board) in his article on the importance of drug compliance in the effective treatment of epilepsy. This article reports on an interesting study involving Episenta – a form of sodium valproate that is packaged as minitables, each one of which is a prolonged delivery unit containing 3mg of the drug and which can therefore be used once-a-day. This is a challenging article as for most of us in clinical practice, we often forget about compliance as a factor in failed medical therapies for neurological disease, including the control of epilepsy.

In our neuropathology series, Kathreena Kurian discusses recent advances in glioma biology, including a detailed discussion of the cancer stem cell that lies at the heart of these tumours. A concept that opens up a radically different therapeutic approach through using techniques and therapies that force these stem cells to undergo a differentiation programme, and by so doing lose their malignant potential. This coupled to a detailed discussion on the genetics and epigenetics of gliomas completes a thoroughly interesting account of one of the most difficult of tumours to treat.

The Rehabilitation article in this issue touches upon a difficult area of clinical practice, the transition of patients from the paediatric to the adult health care system. Often the impact of such changes is not appreciated by those who sit on either side of the divide and Professor Magid Bakheit on behalf of an expert panel discusses this transition with respect to cerebral palsy. They provide a useful table on what is minimally required as opposed to what would be ideal in such a process, and the discussion that revolves around this, could equally well apply to most areas of neurological practice and rehabilitation.

In his ongoing series of articles on Headache in the Neurological literature series, Andrew Larner describes the range of approaches that have been recommended by various authors over the years – including a rather definitive approach by Charles Dickens! As with all his articles, one cannot but be impressed by the detail and knowledge of literature that Andrew displays.

Talking of literature, we are also very fortunate to have an account by (Sir) Terry Pratchett on his dementia and how it presented and came to be diagnosed. This article, which he originally wrote for the Alzheimer's Society (and which they have kindly allowed us to reproduce), is a very eloquent account of how this disease can creep up on individuals and rob them of certain faculties, whilst allowing them to function entirely normally in other areas of life. I would strongly recommend that you read this moving and challenging account.

Finally we have all our usual reviews and once again I would encourage you to become an active member of this journal through either reviewing journals and/or conferences for ACNR as well as providing us with feedback and suggestions. ♦

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

Life with epilepsy can be much more than just a gap between seizures

It's hard to live life to the full if part of you is always expecting the next seizure. NEW VIMPAT® is an anti-epileptic drug with an innovative mode of action.^{1,2} In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.³ Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.^{1,3}

**VIMPAT**[®]
lacosamide

Confidence of additional seizure control

ABBREVIATED PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing). **VIMPAT 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets** **VIMPAT 15 mg/ml syrup** **VIMPAT 10 mg/ml solution for infusion**
Active Ingredient: Tablets: lacosamide 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets. Syrup: lacosamide 15 mg/ml. Solution for infusion: lacosamide 10 mg/ml. **Therapeutic Indications:** VIMPAT is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** Adults and adolescents from 16 years: Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). For solution for infusion: Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. Elderly: No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. Paediatric patients: Not recommended. Patients with renal impairment: No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended in SPC for patients with severe renal impairment and patients with end-stage renal disease. Dose titration should be performed with caution. Patients with hepatic impairment: No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if VIMPAT has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Contraindications, Warnings etc.: **Contraindications:** Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for tablets, hypersensitivity to peanuts or soya. **Precautions:** Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the syrup may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of VIMPAT on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, balance disorder, abnormal coordination, memory

impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. Solution for infusion: Do not store above 25°C. Use immediately. **Legal Category:** POM. **Product Licence Numbers:** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £9.01; 100 mg x 14 tabs: £18.02; 100 mg x 56 tabs: £72.08; 150 mg x 14 tabs: £27.03; 150 mg x 56 tabs: £108.12; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Name and Address of PL Holder:** UCB Pharma S.A., Allee de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformation@ucb-group.com. **Date of Revision:** September 2008. VIMPAT is a registered trade name. **References:** 1. VIMPAT® Summary of Product Characteristics. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** 08VPE0187 November 2008.



Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to UCB Pharma Ltd.

The Ketogenic Diet



**J Helen Cross,
MB, ChB, PhD, FRCP,
FRCPC,**

is the Prince of Wales's Chair of Childhood Epilepsy at UCL-Institute of Child Health, Great Ormond Street Hospital & National Centre for Young People with Epilepsy. Her research interests include neuroimaging as well as the role of early surgical intervention and new treatments in childhood epilepsy. In addition she is involved in national and international collaborations in the development of epilepsy services, teaching and research.

Correspondence to:
UCL-Institute of Child Health,
The Wolfson Centre,
Mecklenburgh Square,
London WC1N 2AP.

The ketogenic diet is a high fat low carbohydrate diet that has been used for almost one hundred years in the treatment of epilepsy. Starvation was originally determined to be beneficial for epileptic seizures.¹ Since this was not a practical solution, the ketogenic diet was devised to mimic the effects of starvation by taking the main energy source as fat. The use of the diet was thereafter first reported for the treatment of seizures in 1921.²

Over the years the Classical ketogenic diet based on the ratio of fat to carbohydrate (including protein) was used (usually 3 or 4:1). This however became less in favour with the advent of anticonvulsant medication. It was also heralded to be 'unpalatable' and causing many side effects. With the realisation however that not all children responded to anticonvulsant medication, interest was maintained in certain centres. In the early 1970s, Huttenlocher reported on a further type of ketogenic diet, still high in fat and low in carbohydrate but using medium chain triglyceride (MCT) oil to supplement each meal and boost ketosis.³ MCT is absorbed more efficiently than long chain fat and is carried directly in the liver. The 'MCT' diet was therefore born. The diet has continued to be used in childhood epilepsy for drug resistant cases, with increased recognition that it is the treatment of choice for certain metabolic disorders. A high level of monitoring is required; not least calculation of the diet requirements specific to each individual child along with appropriate mineral and vitamin supplementation. However dietetic resources have remained scarce. To date the rationale for lack of support has been the paucity of data supporting true efficacy, this despite many open label studies more than suggesting benefit.^{4,5}

Does it work?

Much of the data accumulated on the efficacy of the ketogenic diet in epilepsy has been from open label cohort studies. A systematic review reported in 2000 was concerned about the possible availability and inclusion of only 11 studies, all of which were observational, only 2 of which were prospective and 9 of which were from a single centre with no evidence from randomised controlled trials. This was further highlighted by the Cochrane review, that concluded that there was no reliable evidence from randomised controlled trials to support the use of the ketogenic diet.⁶ This aside, open label studies have consistently reported that 20-40% children have a >90% improvement and a further 20-60% a >50% improvement. A more recent systematic review that only included trials with up to 6 months follow-up again commented on the lack of data



Blueberry muffins
courtesy of Matthews Friends - matthewsfriends.org

from a randomised controlled trial.⁷ However, from a total of 26 studies they were able to include 14, with a collective study population of 972 patients. At 6 months 15.6% were seizure free and 33% had a >50% reduction in seizures. A further meta-analysis found 19/392 abstracts to fulfil inclusion criteria, with a collective population of 1084. They calculated a pooled odds ratio using a random effect model of treatment success amongst patients staying on the diet relative to discontinuation of 2.25 (1.69-2.98).⁸

Recently the first randomised controlled trial comparing the ketogenic diet against no change in treatment has been published.⁹ This study reported on the three month seizure outcome in children with drug resistant epilepsy randomised to either receive a ketogenic diet after 4 weeks baseline or after a further 3 months during which there was no change in treatment. This showed responder rates on an intention to treat basis of 38% when compared to 6% in the no change group. Further 7% on the diet had a >90% reduction compared to none in the control group. These showed rates of response comparable to any new anticonvulsant medication, in a relatively drug resistant group, providing long awaited definitive evidence for its benefit. As part of the trial protocol, the ketogenic diet group were further randomised to receive either the MCT diet or the classical diet; results showed there was no significant difference in the responder rates or mean reduction in seizure frequency between the two groups.¹⁰ This would suggest that not only is the ketogenic diet an appropriate treatment to discuss after failure of two anticonvulsant medications but also that a degree of dietetic and parent choice can be undertaken as to which diet may be used.

How does it work?

Over the years many attempts have been made from clinical summation and animal studies

Same... yet different



Up to 16 weeks between injections and ready-to-use¹


NeuroBloc[®]
Botulinum Toxin Type B Injectable Solution 5,000U/mL

Adds efficiency to efficacy. That's smart.

ABBREVIATED PRESCRIBING INFORMATION

NeuroBloc[®] (Botulinum toxin Type B)

Please refer to the SPC before prescribing.

Presentation: 0.5ml, 1ml and 2ml vials containing 2500U, 5000U and 10000U of Botulinum Toxin Type B solution for injection.

Indication: Treatment of cervical dystonia (torticollis).

Dose and administration: For intramuscular (IM) administration only. Must only be administered by experienced physicians. When low doses are required, it must be diluted before use with preservative-free 0.9% sodium chloride solution for injection. Dosage units are specific to botulinum Toxin Type B only and are not relevant to preparations of Botulinum Toxin Type A. See SPC for instructions for use and handling.

Adults and elderly: 5000U or 10000U divided between two to four affected muscles. 10000U may increase the clinical benefit. The dose and frequency of administration should be adjusted for each patient depending on the clinical response.

Patients with renal or hepatic impairment: No dose adjustment required. (see SPC)

Children and adolescents under 18 years: Not recommended

Contra-Indications: Hypersensitivity to Botulinum Toxin Type B or any excipient. Individuals with other neuromuscular diseases or neuromuscular junctional disorders.

Pregnancy: Do not use during pregnancy unless clearly necessary. Studies in animals are insufficient and potential risk in humans is unknown.

Lactation: Do not use during lactation unless clearly necessary as it is unknown whether Botulinum Toxin Type B is excreted in breast milk.

Warnings and Precautions: Caution should be exercised to prevent administration into a blood vessel. Caution should be used in patients with bleeding disorders or receiving anticoagulant therapy.

Neuromuscular side effects due to toxin spread have been reported. Development of an immune response and subsequent tolerance can occur after repeated administration. Spontaneous reports of dysphagia, aspiration pneumonia and/or potentially fatal respiratory disease, after treatment with Botulinum Toxin Type A/B have been reported. There is an increased risk of side effects in patients with underlying neuromuscular disease and swallowing disorders. Close medical supervision is advised in patients with neuromuscular disorders or history of dysphagia and aspiration. Seeking medical attention for respiratory difficulties, choking or any new or worsening dysphagia is advised. Dysphagia has been reported following injection to sites other than the cervical musculature. Botulinum Toxin Type B contains human albumin and therefore the possibility of transmitting infectious agents cannot be totally excluded. Dosage units are specific to Botulinum Toxin Type B only and are not relevant to preparations of Botulinum Toxin Type A.

Drug Interactions: No specific interaction studies. Effect of co-administration with other botulinum toxin types is unknown. Co-administration of Botulinum Toxin Type B and aminoglycosides or agents interfering with neuromuscular transmission (e.g. curare-like compounds) should be considered with caution.

Side effects: Adverse reactions reported with Botulinum Toxin Type B (toxin-naïve and toxin-responsive) are: Very common (≥1/10): dry mouth, dysphagia, headache and injection site pain. Common (≥1/100 to <1/10): worsening of torticollis (from baseline), torticollis, taste perversion, voice alteration, dyspepsia, myasthenia, blurred vision, neck pain, dysphonia and injection site pain. Electrophysiological jitter, which is not associated with clinical weakness or other electrophysiological abnormalities, may be experienced in some distant muscles. There have been post marketing reports of exaggerated muscle weakness, dysphagia, aspiration, pneumonia with fatal outcome in some cases, abnormal accommodation, ptosis, vomiting, constipation, flu-like symptoms, and asthenia.

Shelf-life: 3 years. Chemical and physical in use stability has been demonstrated for up to 8 hours at 25°C
Special precautions for storage: 2°C – 8°C. Do not freeze. Protect from light. For storage conditions of the diluted medicinal product, see SPC

Legal Category: POM

Basic UK NHS cost: Botulinum Toxin Type B 0.5ml vial: £111.20, Botulinum Toxin Type B 1ml vial: £148.27 and Botulinum Toxin Type B 2ml vial: £197.69

Irish price to wholesaler: Botulinum Toxin Type B 0.5ml vial: €152.55; Botulinum Toxin Type B 1ml vial: €203.40 and Botulinum Toxin Type B 2ml vial: €271.19

Marketing authorisation numbers: Botulinum Toxin Type B 0.5ml vial: EU/1/00/166/001 Botulinum Toxin Type B 1ml vial: EU/1/00/166/002 and Botulinum Toxin Type B 2ml vial: EU/1/00/166/003

Marketing authorisation holder: Eisai Ltd, 3 Shortlands, Hammersmith, London, W6 8EE, United Kingdom

Further information from: Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE

Date of preparation: March 2008

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

References: 1. NeuroBloc Summary of Product Characteristics.



Eisai code: NEU-1072.
Date of preparation: March 2008.

under license from
SOLSTICE
NEUROSCIENCES

about the possible mechanism of action of the ketogenic diet.^{11,12} It may be that a single action is not responsible for its effect. Several biochemical changes that result from the diet have been advocated as possibly involved in the anticonvulsant action including ketone bodies, free fatty acids (especially polyunsaturated fatty acids) or glucose restriction.¹² A link between ketosis and seizure control has both been proved and disproved; although there is evidence of ketones having anticonvulsant properties, optimal seizure control generally lags days to weeks behind the development of ketonaemia which occurs within hours of diet onset. Calorie restriction alone has been demonstrated in mice to impair seizure susceptibility. Some evidence suggests this may activate ATP sensitive potassium channels that may critically be involved in the regulation of seizure activity. Other evidence has suggested this may be boosted by free fatty acid accumulation. There are also hypotheses with regard to neurotransmitters. Much animal data has been accumulated, a full review of which is available elsewhere.¹²

Indications

In general, there is no reason why the ketogenic diet cannot be considered after failure of two appropriate antiepileptic medications in the treatment of childhood epilepsy. One particular question that remains however is are there particular individuals who are more likely to respond than others, and therefore should be trialed on the diet earlier rather than later? Open label studies have reported benefit in several epilepsy syndromes, particularly in myoclonic astatic epilepsy,¹³ Dravets syndrome,¹⁴ and tuberous sclerosis.^{15,16} This aside, in the randomised controlled trial reported by Neal and colleagues, no difference in efficacy was seen between focal and generalised epilepsy; more specific breakdown into individual syndromes demonstrated little benefit in one over another, not surprisingly in view of the small numbers in each group.⁹

Of course there remain metabolic defects, of which seizures may be part of the clinical phenotype, where the ketogenic diet is imperative in treatment as the ketones provide the energy source. An example would be glucose transporter defects, where glucose uptake is poor into the central nervous system and ketones provide an alternative fuel. The diet would appear important for a child to adhere to during periods of brain development but the need beyond this remains unclear.¹⁷

The ketogenic diet has now been shown to be as effective as any new anticonvulsant drug in drug resistant childhood epilepsy

Side effects and contraindications

As with any anticonvulsant drugs there remain side effects. The diet cannot be considered a 'natural' treatment. This aside, although studies suggest a high rate of side effects, few children discontinue the diet because of these, as dietary adjustment can usually resolve them. In the randomised controlled trial published by Neal et al⁹ the most common side effects after three months of the diet were vomiting (13/54, 24%), constipation (18/54, 33%), lack of energy (13/54, 24%), hunger (12/54, 22%) and diarrhoea (7/54, 13%). However only 10/65 children who received the diet discontinued because of side effects prior to three months; three because of parental unhappiness with the restrictions, two with behavioural food refusal, and one each with increased seizures, extreme drowsiness, constipation, vomiting and diarrhoea. Renal stones are a theoretical risk; a study from the John Hopkins group has suggested young children with a high calcium excretion are those most at risk.¹⁸ Furthermore, growth may be delayed; it appears growth velocity deviates more from the expected trajectory the longer an individual is on the diet, particularly in the young.^{19,20} This appears to be true regardless of the type of diet used.¹⁹

There are few contraindications to use of the diet. There are of course certain metabolic defects that must be excluded as the individual requires glucose for energy metabolism, such as the organic acidurias, including pyruvate carboxylase deficiency. Furthermore, although behaviour disorder per se would not be considered a contraindication, behaviour difficulties specifically related to eating should be resolved as much as possible before considering this form of treatment. Gastroesophageal reflux may of course be exacerbated in view of delayed gastric emptying from the high fat content of the diet.

When should the diet be used in epilepsy?

The diet cannot be thought of as a natural treatment; it has side effects just as any other anticonvulsant medication as outlined above. This aside it has now been demonstrated that it can be effective in

drug resistant epilepsy when compared to no change in treatment. It should therefore be considered earlier in the natural history of childhood epilepsy when initial response to antiepileptic drugs is not seen. However, the diet requires a high level of dietetic and medical monitoring. The lack of wider availability relates to shortage of dietetic support which needs to be addressed in the long term. ♦

REFERENCES

1. Guelpa GMA. *La lutte contre l'épilepsie par la désintoxication et par la réduction alimentaire*. Revue de Therapie Medico-Chirurgicale 1911;78:8-13.
2. Wilder RM. *The effects of ketonemia on the course of epilepsy*. Mayo Clin Proc 1921;2:307-8.
3. Huttenlocher PR, Wilbourn AJ, Signore JM. *Medium-chain triglycerides as a therapy for intractable childhood epilepsy*. Neurology 1971;21:1097-1103.
4. Freeman JM, Vining EPG, Pillas DJ. *The efficacy of the ketogenic diet - 1998: a prospective evaluation of intervention in 150 children*. Pediatrics 1998;102:1358-63.
5. Kang HC, Kim YJ, Kim HD. *Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multi-centre experience*. Epilepsia 2005;46:272-79.
6. Levy R, Cooper P. *Ketogenic diet for epilepsy* (Cochrane review). The Cochrane Library [3]. 2004. Chichester, UK, John Wiley & Sons.
7. Keene DL. *A systematic review of the use of the ketogenic diet in childhood epilepsy*. Pediatr Neurol 2006;35:1-5.
8. Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. *Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis*. J Child Neurol 2006;21:193-8.
9. Neal EG, Chaffe HM, Schwartz RH et al. *The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial*. Lancet Neurol 2008;7:500-6.
10. Neal EG, Chaffe HM, Schwartz RH et al. *A randomised controlled trial of classical and medium chain triglyceride ketogenic diets in the treatment of childhood epilepsy*. Epilepsia 2008;49:1-9.
11. Hartman A, Gasior M, Vining EP, Rogawski MA. *The neuropharmacology of the ketogenic diet*. Pediatr Neurol 2007;36:281-92.
12. Bough KJ, Rho JM. *Anticonvulsant mechanisms of the ketogenic diet*. Epilepsia 2007;48:43-58.
13. Oguni H, Tanaka T, Hayashi K, et al. *Treatment and long term prognosis of myoclonic astatic epilepsy of early childhood*. Neuropediatrics 2002;33:122-32.
14. Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. *Ketogenic diet in patients with Dravet syndrome*. Epilepsia 2005;46:1539-44.
15. Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM. *Tuberous sclerosis complex and the ketogenic diet*. Epilepsia 2005;46:1684-6.
16. Coppola G, Klepper J, Ammedola E et al. *The effects of the ketogenic diet in refractory partial seizures with reference to tuberous sclerosis*. Eur J Paediatr Neurol 2006;10:148-51.
17. Klepper J, Leidencker B. *GLUT1 deficiency syndrome-2007 update*. Dev Med Child Neurol 2007;49:707-16.
18. Furth SL, Casey JC, Pyzik PL et al. *Risk factors for urolithiasis in children on the ketogenic diet*. Pediatr Nephrol 2000;15:125-8.
19. Neal EG, Chaffe HM, Edwards N, Lawson M, Schwartz R, Cross JH. *Growth of children on classical and medium chain triglyceride ketogenic diets*. Pediatrics 2008;In press.
20. Vining EP, Pyzik PL, McGrogan JR et al. *Growth of children on the ketogenic diet*. Dev Med Child Neurol 2002;44:796-802.

Today, unnecessary seizures restrict 69,000 lives!



The chance to control seizures, not lives

ABBREVIATED PRESCRIBING INFORMATION

Zonegran® (zonisamide)

Please refer to the SmPC before prescribing.

Presentation: Hard capsules containing 25 mg, 50 mg or 100 mg zonisamide.

Indication: Adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation. **Dose and administration:** **Adult:** Zonegran must be added to existing therapy. Initial daily dose is 50 mg in two divided doses. After one week, increase to 100 mg daily and then at one weekly intervals, in 100 mg increments. Consider two weekly intervals in renal or hepatic impairment and patients not receiving CYP3A4-inducing agents. Zonegran can be administered once or twice daily after the titration phase. Withdraw gradually. **Elderly and patients with renal or hepatic impairment:** Caution (see SmPC). Not recommended in severe hepatic impairment. **Children and adolescents under 18 years:** Not recommended.

Contra-Indications: Hypersensitivity to zonisamide, sulphonamide or any excipient. **Pregnancy:** Zonegran must not be used during pregnancy unless clearly necessary in the opinion of the physician, and only if potential benefits justify risk to the foetus. Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. **Lactation:** Zonisamide is excreted into breast milk. A decision must be made to either discontinue Zonegran or stop breast-feeding. Breast-feeding should not be resumed until one month after stopping Zonegran. **Warnings and Precautions:** Serious rashes occur in association with Zonegran therapy, including cases of Stevens-Johnson syndrome. Zonegran contains a sulphonamide group. Serious immune based adverse reactions are associated with the sulphonamide group, e.g. rash, allergic reaction, major haematological disturbances including aplastic anaemia, which very rarely can be fatal. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Kidney stones have occurred. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, a family history of

nephrolithiasis and hypercalcaemia. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, and consider discontinuation in absence of another cause. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage, e.g. serum creatine phosphokinase and aldolase levels, and consider discontinuation. Zonegran 100 mg hard capsules contain E110, which may cause allergic reactions. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. **Drug Interactions:** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. **Side effects:** The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance: Very common effects ($\geq 1/10$): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects ($\geq 1/100, < 1/10$): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon ($\geq 1/1000, < 1/100$): pneumonia, urinary tract infection, hypokalaemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. Very Rare ($< 1/10,000$ including isolated reports): agranulocytosis,

aplastic anemia, leucocytosis, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia, metabolic acidosis, hallucination, amnesia, coma, grand mal seizure, myasthenic syndrome, neuroleptic malignant syndrome, status epilepticus, dyspnoea, pneumonia aspiration, respiratory disorder, pancreatitis, hepatocellular damage, anhidrosis, erythema multiforme, pruritis, Stevens-Johnson syndrome, rhabdomyolysis, hydronephrosis, renal failure, urine abnormality, blood creatine phosphokinase increased, blood creatinine increased, blood urea increased, liver function tests abnormal, heat stroke. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged 65 years or older report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal Category:** POM. **Presentation:** PVC/PCTFE/aluminium blisters. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €10.95, Zonegran 50 mg: packs of 56 €58.07, Zonegran 100 mg: packs of 56 €77.59. **Marketing authorisation numbers:** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE. **Date of preparation:** June 2008.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Eisai Ltd on 020 8600 1400 or Lmedinfo@eisai.net

Reference

1. All Party Parliamentary Group on Epilepsy. The human and economic cost of epilepsy in England. Published 27th June 2007.

Date of preparation: September 2008. Z2191 09/08



Treatment of Paraneoplastic Neurological Syndromes



Anette Storstein

is consultant neurologist and post-doctorate fellow at Haukeland University Hospital. She runs the neuro-oncology clinic at the Department of neurology and her research interest is neuroimmunology.



Christian Vedeler

is consultant neurologist and professor at the Haukeland University Hospital and University of Bergen. He runs the peripheral nerve clinic at the Department of neurology and his research interest is neuroimmunology.

Correspondence to:

Dr Christian A Vedeler,
Department of Neurology,
Haukeland University Hospital,
N-5021 Bergen, Norway.
Email: christian.vedeler@helse-bergen.no

Paraneoplastic neurological syndromes (PNS) are rare complications of cancer that often herald the tumour diagnosis. Whereas some syndromes affect only certain parts of the nervous system, other syndromes involve both central and peripheral neurons, resulting in complex clinical manifestations.¹ The syndromes are believed to be immune-mediated, caused by T cell, B cell and macrophage responses to antigens present on tumour cells and on neurons and glia cells (Figure 1).² Activation of B cells results in the production of onconeural antibodies that are highly useful diagnostic markers for a paraneoplastic aetiology. According to diagnostic criteria, the presence of a well-characterized onconeural antibody in a patient with neurological symptoms defines the disease as paraneoplastic even in the absence of detectable malignancy.³ Onconeural antibodies are detected in about 60% of patients with PNS. PNS and onconeural antibodies have been discussed in a previous review in this journal.⁴

The symptoms as well as the severity of the PNS are heterogenous, depending on which parts of the peripheral and central nervous system are affected. Some syndromes have a high mortality rate, such as paraneoplastic

encephalomyelitis and brain stem encephalitis, whereas other syndromes are less lethal but leave the patients with disabling neurological deficits, such as paraneoplastic cerebellar degeneration and peripheral neuropathy. The rapidly progressive and often dramatic nature of the PNS symptoms requires urgent therapeutic considerations. Nevertheless, the rarity of PNS limits the number of published therapy studies, in particular studies with a prospective design. Thus, there is no class I or II evidence for PNS therapy except for the syndromes that affect the neuromuscular junction (paraneoplastic myasthenia gravis, Lambert-Eaton myasthenic syndrome, and neuromyotonia). Many patients receive concomitant anti-neoplastic therapy and immunotherapy, but so far there is no standard care for any of the PNS. This review focuses on the therapeutic options of PNS, but does not include the autoimmune neuromuscular diseases.

Anti-neoplastic therapy

The cornerstone of PNS therapy is resection of the tumour and/or oncological treatment, in order to eradicate the systemic antigenic source. Tumour removal is an independent predictor of

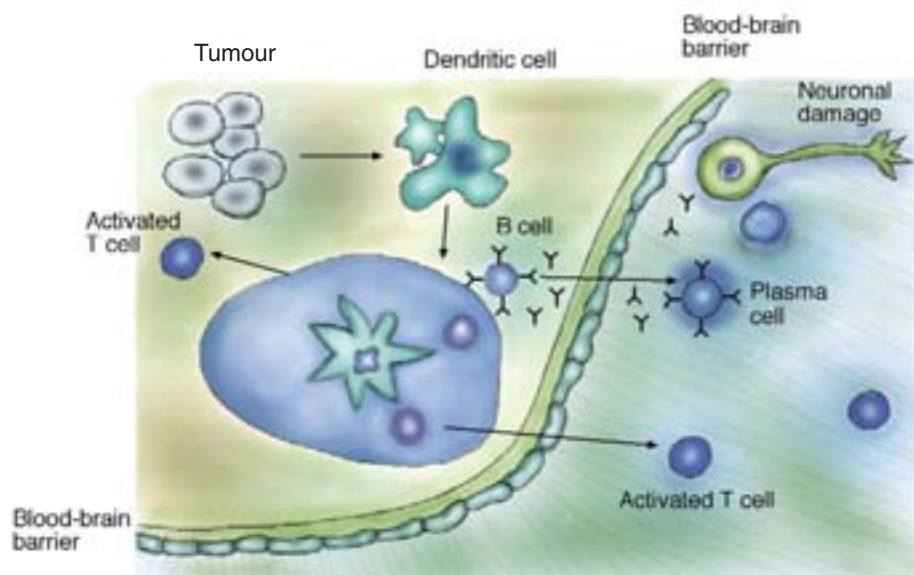


Figure 1: Plasma cells and cytotoxic T cells can cross the blood-brain-barrier and react with antigens shared by tumour cells and cells of the nervous system (onconeural antigens).

Table 1: Paraneoplastic neurological syndromes (PNS) and response to therapy

PNS	Tumour therapy	Immunotherapy	Symptomatic therapy
LE	Yes, especially when treated early	Variable. Patients with VGKC /NMDA antibodies respond best	Yes
SSN	Yes, especially when treated early	Rare	Yes
CD	Yes, especially in Hodgkin's	Rare	Yes
O-M	Yes	Often in children. Occasionally in adults.	Yes

LE: Limbic encephalitis; SSN: Subacute sensory neuropathy; CD: Cerebellar degeneration; O-M: Opsoclonus-myoelonus.

Early diagnosis of PNS is of great importance to obtain the best results of treatment. The cornerstone of PNS treatment is resection of the tumour and/or oncological treatment

improvement or stabilization in PNS patients.⁵ Thus, malignancy screening should be prompt and thorough in all patients with a suspected PNS. If conventional radiological examinations fail to detect cancer, a FDG-PET scan should be performed to increase the sensitivity for detection of small tumours or mediastinal lymphadenopathy.⁶ The sensitivity of FDG-PET is poorer in antibody-negative patients.

None of the onconeural antibodies are 100% organ-specific, but the identification of one of the well-characterized antibodies often indicates the most likely sites of malignancy. Exploratory surgery to diagnose occult malignancy may be considered in selected antibody-positive patients. For instance, orchiectomy in young males with Ma2-antibody associated encephalitis resulted in histological confirmation of cancer.⁷

In most cases, an aggressive diagnostic approach will result in cancer detection. If possible, histological verification of malignancy should be obtained, and expression of the relevant antigen should be confirmed to exclude the possibility of a second cancer. If complete malignancy screening, including whole-body FDG-PET is negative, we recommend immunotherapy and repeated investigations within 6 months.⁸

Immunotherapy

Given the immune-mediated pathogenesis of PNS, concomitant immunotherapy is administered to most patients. This includes plasmapheresis; iv IgG, corticosteroids, cyclophosphamide, tacrolimus and rituximab. The response to immunotherapy in PNS is highly variable, and patients with involvement of the peripheral nervous system usually respond

better compared to patients with manifestations from the central nervous system.⁹ This difference is largely due to the fact that paraneoplastic synaptic disorders of the peripheral nervous system are caused by antibodies that are pathogenic, e.g. paraneoplastic Lambert-Eaton syndrome, neuromyotonia and myasthenia gravis which are caused by VGCC, VGKC and AChR/Musk antibodies, respectively. The antigen targets of these antibodies are located in or in close proximity to the cell membrane. The immunotherapy regimens used in these disorders exert their main beneficial effects by lowering the amount of circulating antibodies, as well as suppressing the local immune response in the neuromuscular junction. Treatment of autoimmune neuromuscular diseases is reviewed elsewhere.¹⁰

PNS affecting the central nervous system are usually more or less refractory to treatment with immunotherapy. This can be explained by several factors, including the T cell dominated immune response, the blood-brain-barrier and the limited potential of regeneration of the central nervous system. Even if immunotherapy results in a decline in serum antibody titres, this is seldom associated with clinical improvement. Therefore, serial determination of antibodies cannot be used to monitor neurological outcome or tumour evolution in PNS.¹¹

Patients with paraneoplastic cerebellar degeneration associated with Yo or Hu antibodies are usually unresponsive to immunotherapy, although there are case reports of an apparent benefit of treatment with rituximab.¹² Such clinical responders have often had a short duration of neurological symptoms. Paraneoplastic opsoclonus-myoelonus is the only PNS that affects paediatric patients with associated neuroblastoma.

Whereas adult patients with paraneoplastic opsoclonus-myoelonus only occasionally benefit from immunotherapy, children may respond quite well to high-pulse dexamethasone and other immunosuppressive regimens.¹³

Among the PNS affecting the central nervous system, limbic encephalitis constitutes a heterogeneous group of disorders, of which some have a more favourable response to immunotherapy. As recently pointed out by Dalmau and Rosenfeld, limbic encephalitis should be classified into subphenotypes according to the location of the target antigens.¹ Limbic encephalitis associated with Hu, Ma2, CRMP5 or amphiphysin antibodies rarely respond to immunotherapy, although patients with testicular cancer and Ma2 antibodies seem to have a more favourable prognosis. On the other hand, patients with associated VGKC or NMDA antibodies benefit from immunotherapy.¹

In general, the effect of immunotherapy in PNS of the central nervous system seems to depend upon the severity as well as the duration of the neurological symptoms.¹⁴ Most PNS have a subacute onset and stabilization within the course of a few months. Even patients with PNS and a pronounced neuronal loss, as paraneoplastic cerebellar degeneration, have been shown to respond to immunotherapy when administered very early on in the disease.¹⁶ This indicates that an acute stage of inflammation precedes irreversible neuronal damage. Immunotherapy should therefore be administered concomitantly with anti-neoplastic therapy as early as possible. However, there are no absolute guidelines for the priority of the different immunotherapy regimens.

Symptomatic treatment

Many PNS patients have disabling neurological symptoms, and the need for supplementary symptomatic treatment should be evaluated in all patients. This includes physical therapy, speech therapy for patients with cerebellar or brain stem dysfunction; antidepressants, neuroleptics or antiepileptic medication for limbic encephalitis; analgesics, antidepressants or antiepileptic drugs for neuropathic pain, as well as supportive therapy. Autonomic dysfunction, which often occurs in patients with subacute sensory neuronopathy, should also be treated.⁸

Conclusions

Early diagnosis of PNS is of great importance to obtain the best results of treatment. The cornerstone of PNS therapy is resection of the tumour and /or oncological treatment. PNS are associated with various onconeural antibodies, and the response to concomitant immunotherapy depends on the location of the target antigens. PNS with onconeural antibodies against cell-surface antigens, in particular the neuromuscular diseases, usually respond to immunotherapy, whereas PNS with onconeural antibodies against intracellular antigens are usually refractory to such therapy. ♦

REFERENCES

- Dalmau J, Rosenfeld MR. *Paraneoplastic syndromes of the CNS*. *Lancet Neurol* 2008;7:327-40.
- Storstein A, Vedeler CA. *Paraneoplastic neurological syndromes and onconeural antibodies: clinical and immunological aspects*. *Adv Clin Chem*. 2007;44:143-85.
- Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler C, Verschuur J, Vincent A, Voltz R. *Recommended diagnostic criteria for paraneoplastic neurological syndromes*. *J Neurol Neurosurg Psychiatry*. 2004;75:1135-40.
- Vincent A, Bien C. *Paraneoplastic neurological diseases*. *ACNR* 2007;7:6-8.
- Keime-Guibert F, Graus F, Broët P, Reñé R, Molinuevo JL, Ascaso C, Delattre JY. *Clinical outcome of patients with anti-Hu-associated encephalomyelitis after treatment of the tumor*. *Neurology*. 1999;53:1719-23.
- Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, Ternamian PJ, Trouillas P, Honnorat J. *FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes*. *Brain*. 2004;127:2331-8
- Mathews RM, Vandenbergh R, Garcia-Merino A et al. *Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis*. *Neurology* 2007;68:900-5.
- Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevs Smitt PA, Verschuur JJ, Voltz R. *Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force*. *Eur J Neurol*. 2006;13:682-90.
- Uchuya M, Graus F, Vega F, Rene R, Delattre JY. *Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies*. *J Neurol Neurosurg Psych* 60:388-92.
- Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuur J, Horge HW. *Guidelines for the treatment of autoimmune neuromuscular transmission disorders*. *Eur J Neurol* 2006;13:691-9.
- Lladó A, Mannucci P, Carpentier AF, Paris S, Blanco Y, Saiz A, Delattre JY, Graus F. *Value of Hu antibody determinations in the follow-up of paraneoplastic neurologic syndromes*. *Neurology*. 2004;63:1947-9.
- Shamsili S, de Beukelaar J, Gratama JW, Hooijkaas H, van den Bent M, van 't Veer M, Sillevs Smitt P. *An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes*. *J Neurol*. 2006;253:16-20.
- Ertle F, Behnisch W, Al Mulla NA, Bessiso M, Rating D, Mechttersheimer G, Hero B, Kulozik AE. *Treatment of neuroblastoma-related opsoclonus-myoclonus-ataxia syndrome with high-dose dexamethasone pulses*. *Pediatr Blood Cancer*. 2008;50:683-7.
- Blaes F, Strittmatter M, Merkelbach S, Jost V, Klotz M, Schimrigk K, Hamann GF. *Intravenous immunoglobulins in the therapy of paraneoplastic neurological disorders*. *J Neurol*. 1999;246:299-303.
- Widdess-Walsh P, Tavee JO, Schuele S, Stevens GH. *Response to intravenous immunoglobulin in anti-Yo-associated paraneoplastic cerebellar degeneration: case report and review of the literature*. *J Neurooncol* 2003;63:187-90.

SIGGI II

Pocket-sized Signal Generator

For use in Neurophysiology, Neurology, rehabilitation, psychiatry & research

Applications:

- Electrode Tester
- Signal generator including trigger; noise overlay on demand
- Impedance meter with simultaneous display of electrode potential.
- AC – and DC – amplifier and – recorder.



020 8543 0022
 sales@brainvision.co.uk
 www.brainvision.co.uk

For more information please contact: Brain Vision (UK) Ltd
 Suite 4, Zeal House
 8 Deer Park Rd. London SW19 3GY

**MagVenture
 MagPro Series of
 magnetic
 stimulators**

For use in Neurophysiology, Neurology, rehabilitation, psychiatry & research

Applications:

- Motor Evoked Potentials with built in MEP monitor on selected models
- Transcranial magnetic stimulation (TMS)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Functional Magnetic Stimulation (FMS)
- Dynamic Coils, Static coils (fluid filled) & fMRI Compatible coils



**TSA II Neuro
 Sensory
 Analyzer**

The Essential Tool in Sensory Nerve Evaluation



“QST of the thermal modalities is the only clinical test for quantitative assessment of small caliber sensory nerve fiber function, the primary transmitters of pain sensation”

Improving the Effectiveness of Drugs in Epilepsy Through Concordance



**Professor
Hermann Stefan**

is Director of the Epilepsy Centre in Erlangen.

Correspondence to:
Professor Hermann Stefan
Neurological University Hospital
Epilepsy Centre
Schwabachanlage 6
91054 Erlangen, Germany

Statement of financial support:
The post-marketing surveillance study on sustained release valproate was carried out and financed by the company Desitin Arzneimittel GmbH, Hamburg.

Compliance with a prescribed medicine regimen is a ubiquitous problem not confined to the treatment of asymptomatic conditions. Despite this, the poor compliance in patients with epilepsy is somewhat surprising given that patients are aware of the serious consequences in terms of seizures and even death. In this context it is important that we look for ways to improve epilepsy patients' adherence to the prescribed medication as a way of improving outcome.

Compliance in Epilepsy

A survey undertaken by Neurologists (n=661) in the USA¹ revealed that 71% of patients with epilepsy forgot to take their AED (anti-epileptic drug) at least once per month and it was evident that the chance of a patient missing a dose increased with the number of tablets prescribed. Of patients that missed a dose 45% reported a seizure. Patients taking a larger number of tablets/capsules increased their odds of having a seizure after a missed dose by 43%.

Similar results were reported in a recent UK study² which revealed that 59% of epilepsy patients had poor compliance and that this was related to an increased frequency of seizures.

A study in Germany³ measured post-ictal serum levels of anti-epileptic medications and confirmed that in at least 44% of cases the seizure was related to poor compliance.

A review of 10,892 epilepsy patients in a USA managed care system⁴ revealed that poor adherence was associated with a 11% increase in hospitalisation and a 47% increase in emergency admissions and as a consequence there was significantly increased healthcare costs.

It is evident that if a patient's seizures are not controlled by one AED there may be no point changing to another if the reason for lack of efficacy is non-compliance. Key conclusions from these studies are that the assessment of compliance should be a routine part of the management of epilepsy and physicians should consider prescribing the simplest regimen with the fewest daily doses and tablets.

The importance of seizure control

With optimal AED therapy up to 70% of people with epilepsy can expect to become seizure free⁵ but inadequate management results in uncontrolled seizures, drug side effects, psychological and physical morbidity and an increased risk of premature death.^{6,7}

In the UK more than 1000 people die each year because of epilepsy and most of these deaths are associated with seizures.⁶ Sudden unexpected death in epilepsy (SUDEP) is the principal cause of death in people with chronic epilepsy.⁶ Patients with a history of seizure in the previous year have a 23-fold increased risk of SUDEP compared to people with fully controlled seizures, and the risks increase with increasing seizure frequency.⁸

Non-compliance significantly increases the risk of seizure, A&E visits, hospitalisation, road traffic accidents, fractures and death⁹ and is therefore a key contributor to suboptimal management.

Issues related to poor compliance

There are many factors that influence compliance in people with epilepsy but the frequency, type and severity of seizures do not in themselves

Adherence is an important precondition for efficacy of long-term epilepsy treatment

Factors influencing medicine taking in children and young people with epilepsy (Adapted from WHO ¹⁴)		
Type of factor	Factors and their influence	
	Positive	Negative
Patients	satisfaction with medical care not feeling stigmatised by epilepsy feeling that it is important to take the medicine high levels of stressful life events	disbelief/denial of the diagnosis refusal to take any medication delusional thinking inconvenience of treatment lifestyle and health beliefs influence by relatives fear of addiction uncertainty about the need for drugs anxiety over the complexity of the regimen feeling stigmatised by the epilepsy
Epilepsy		forgetfulness due to impaired memory previous treatment failures frequent seizures
Treatment	single AED with simple dosing schedule	complex regimens misunderstanding how to take the AED side-effects
Health professionals/ healthcare system	good relationship between patient and physician	irregular drug supply lack of education about AEDs.
Socio-economic	parents report less education language barriers lower income recent immigrants	long distance from treatment centre teenager poverty local beliefs about the origins of illness
Note: Some factors identified by WHO have been omitted as not relevant in the UK setting		

appear to influence compliance rates.¹⁰ Irregular requests for repeat AED prescriptions, lack of response to appropriate therapy and an increase in seizure frequency may indicate non-compliance. It is, however, difficult to identify all patients who do not comply with their AED therapy. Health professionals should therefore be alert to the potential for non-compliance in all patients with epilepsy, enquiring non-judgementally about medicine taking at each consultation and being prepared to support patients in complying with their treatment. In addition to the diagnosis of epilepsy in a considerable number of patients depressive mood changes exist. In those patients rates of adherence is reduced and requires special strategies for continuous treatment.¹¹

The patients can have poor compliance if they do not understand the importance of taking their medication, if they experience side-effects, feel stigmatised by their condition, have difficulty in swallowing their medication or have multiple doses.¹² These issues can be multiplied if the patient is on multiple medications for concomitant conditions. Age can also be a factor with compliance being particularly poor in teenagers. Factors influencing compliance in children are highlighted in Table 1. Caring for a child with a learning disability is a major source of stress for parents, and the family situation can be made more difficult by children's behavioural and emo-

tional difficulties that require treatment with drugs that in themselves may increase the risk of seizure.¹³

Although non-compliance in epilepsy may be unintentional, most non-compliance with AEDs is intentional and results from conscious choices by patients.¹ These decisions are based on patients' beliefs about medicines in general that are affected by the experience of family and friends, culture, education, social circumstances, fears and anxieties and may be the result of an incomplete understanding of epilepsy and the proposed treatment. The result may be that patients are unsure that the benefits of AED treatment outweigh the perceived risks of taking medication.¹⁴

Swallowing difficulties

The incidence of patients who have swallowing difficulties may be much higher than generally realised and this can have implications in relation to compliance and subsequent lack of symptom control.¹⁶ The issues related to children may be more widely accepted but recent UK surveys have shown significant issues with dysphagia in the elderly and other patient groups, for example between 29 and 65% of stroke patients are reported to have swallowing difficulties.¹⁶ Swallowing difficulties are common in patients with epilepsy partly because they are exacerbated by concomitant conditions such as mental disability,

stroke or by additional medications (e.g. opioids, corticosteroids, diuretics etc) which may cause dry mouth.

A recent survey conducted by The School of Pharmacy, Bradford University¹⁷ in care homes (n=540) revealed that 22% of patients had swallowing difficulties and 11% regularly spat out medication. A similar audit conducted in elderly patients (n=182) in general practice¹⁸ in 2004 found that 11% of patients had dysphagia. The authors concluded that these findings are of concern and raise serious medicine management issues. There is a need for healthcare workers to enquire more about such issues and aim to provide medicines that are easier to take.

A move towards concordance

Making patients aware of the potential consequences of non-compliance is an important first step, but patient education and empowerment programmes may simply increase knowledge of epilepsy without improving compliance.¹⁹ The approach should not concentrate on instruction and direction about medicine taking, but rather to raise the patients' sense of achieving their own specific goal in dealing with their condition.¹² Adherence can be improved by the following general principles: 1) patient education, 2) improved dosing schedule, 3) increased patient contacts and 4) improved communication.

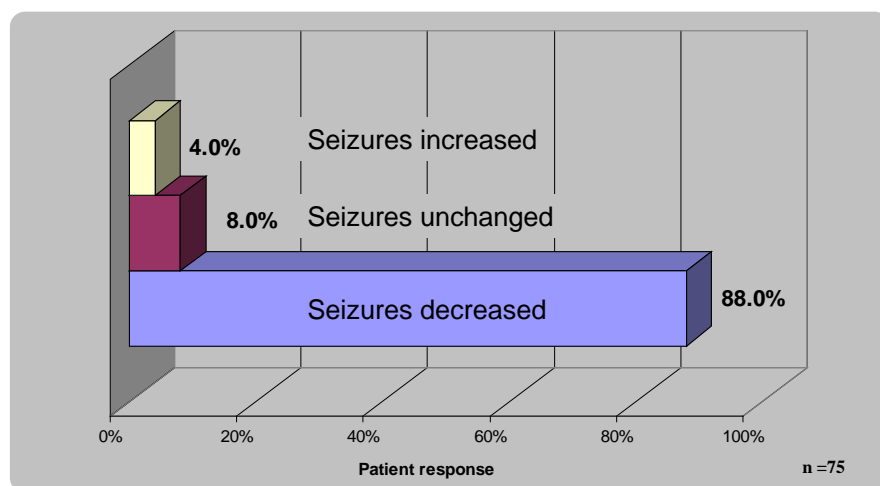


Figure 1: The change in the frequency of seizures in those patients who had seizures prior to being transferred from conventional valproate to valproate minitables (Episenta) taken once daily.

It is with this in mind that clinical guidelines recommend that healthcare professionals adopt a concordant consulting style that enables patients with epilepsy and, where appropriate, their family/carers, to participate as partners in decisions about their health care.²⁰ A two-way process respects the patients' experiences, beliefs and wishes, and enables a mutually agreed decision about medicine taking.

This concordant approach may be difficult to put into practice, but patients are more satisfied and adherent when they are encouraged to talk and perceive that professionals listen to their concerns.²¹

The choice of AED treatment

NICE recommends that AED treatment should be individualised according to each patient's seizure type, epilepsy syndrome, co-medication and comorbidity, lifestyle and preferences,²⁰ and that newer AEDs should only be used in people with epilepsy who have not benefited from or are unsuitable for established drugs such as sodium valproate and carbamazepine.²⁰

Poor compliance, drug interactions and long-term toxicity are all more likely if more than one AED is prescribed.⁵ Patients should therefore be treated with a single AED wherever possible and about 80% of patients can be controlled by a single drug,²⁰ so combination therapy should only be considered when

monotherapy has not resulted in freedom from seizures. If trials of combination therapy do not achieve worthwhile benefits, treatment should revert to the regimen that has proved most acceptable to the individual in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.²⁰

Developing concordance with AEDs

Clinical guidelines provide detailed recommendations about the importance of ongoing counselling, education and support for people with epilepsy and it is essential to ask about practical problems that may reduce compliance, including any difficulties in taking the medicine, side effects or inconvenient AED dosing.

The aim should be to move towards an easy to take once daily medication whenever possible, but many drugs must be taken twice or three times daily. Sodium valproate is recommended and widely used as first-line for all types of seizure so, a means of improving concordance with this product should be welcomed.

Development of improved formulations

It had been recognised that valproate therapy could be limited by gastric intolerance and this led to the introduction of an enteric coated formulation (Epilim) in the 1970's. Sustained-release (SR) formulations enable

once or twice-daily dosing and have the additional advantage of being associated with fewer side-effects.²² In a comparative study (randomised cross over of conventional VPA BID; sustained release BID, once daily morning, once daily evening sustained release (study duration 16 months) patient preference was greatest for once daily evening sustained release VPA.²³

There are, for example, two SR formulations of sodium valproate: a conventional tablet (Epilim Chrono) using technology developed in the early 1990's and one developed to current regulatory guidelines containing many controlled release minitables (Episenta).

Some patients can find it difficult to swallow any conventional tablet, but most conventional sodium valproate SR formulations cannot be crushed because this destroys their prolonged-release effect.²² Liquid formulations are an option, but some young patients do not like the taste, especially if they are on high doses and need to take large volumes. However, with Episenta the capsules or sachets can be opened and the minitables sprinkled onto soft foods or taken with drinks. Each minitablet is a prolonged delivery unit containing 3mg of sodium valproate which can reliably ensure an effective once-a-day treatment to help enhance acceptability to patients with epilepsy. A single evening dose is suitable for most patients.

The eating habits of many patients may vary and this can have significant effects on the bioavailability of some formulations. Altered levels of sodium valproate can result in either more adverse reactions or ineffective treatment. In contrast, the minitables can be taken either before, during or after meals without any affect on absorption as they pass through the pylorus independent of food and do not get retained in the stomach to cause gastric irritation.¹⁰ This type of innovation can make a presentation that is easy to take and can fit into the patients lifestyle in order to improve concordance.

A simple dosage to improve effectiveness

Valproate is widely used as a first line antiepileptic drug in patients with generalised seizures as well as some with focal seizures and patients who may take either conventional or sustained release preparations on a twice

Simplification of drug uptake by once daily application using a slow release formulation supports treatment efficacy

or three times a day dosage. The launch of a version of valproate in an advanced drug delivery system gave us the opportunity of evaluating if patient outcome could be improved by switching to the once daily evening dosage of valproate sustained release minitabets (Episenta).

We conducted a study on 359 epilepsy patients (aged 12 to 86) in Germany;²⁴ the aim of which was to collect data on the use of valproate sustained release minitabets (Episenta) in a once daily evening dosage in patients newly adjusted to the drug or switched from other anti-epileptics, under conditions which are close to those in routine clinical practice. The effect on seizure frequency was of particular interest as well as assessment of adherence to the medication with this simplified therapeutic regimen.

There are methodical limits of an open trial, however, the decisive advantage of open prospective clinical observations is that they reflect routine clinical practice in patients with epilepsy.

Patients were either newly treated with valproate sustained release minitabets (N=58), switched from conventional valproate (N=124) or from sustained release valproate taken twice daily (N=138) to the once daily evening dosing. In 39 patients other antiepileptic drugs were replaced. Patients were entered at the end of a 7-week observational period and then observed for a further 7 weeks.

The once daily evening dosage proved to be effective and well tolerated. It was very well

accepted by patients, as shown by the assessment of the patients themselves and the evaluation of compliance by physicians. It is to be emphasised that the number of seizures with the once daily evening dosage of valproate sustained release minitabets declined on average from 2.1 to 0.5. The number of seizures was reduced not only in the group of newly adjusted patients, but also in those pre-treated with valproate²⁴ (Figure 1). It is notable that the number of seizures in more than 90% of patients who were already being treated with sustained release valproate was reduced still further by the switch to the once daily evening dosage regimen. This is presumably due to better compliance.¹

The valproate sustained release mini-tablets which are in capsules and in sachets, offer particular advantages with regard to their application. The capsules with the sustained release minitabets can be taken whole or after pulling the capsules apart or opening of the sachets in loose form, e.g. in a preferred carbonated drink or sprinkled over soft food such as yoghurt. An additional advantage of the minitabets in contrast to monolithic tablets is that they can be taken independently of meals.

The once daily evening dosage is an important therapeutic option, which together with the above-mentioned advantages of valproate sustained release minitabets leads to greater freedom and improved quality of life for patients. The incidence of seizures was reduced which is probably due to the one

hand to a simplification of the treatment regimen, on the other to more stable serum concentrations.

The results of this post-marketing surveillance study underline the importance of compliance-promoting therapeutic regimens for the effective seizure control. A more timely extended evaluation still is necessary to evaluate the amount and persistence of seizure control over a longer period. Medications that may be regarded as "patient friendly" can help move closer to the goal of concordance.

Conclusion

Non-compliance with AEDs is a major cause of seizures and healthcare professionals are tasked with the responsibility of finding ways to resolve this problem in order to protect patients with epilepsy from the consequences of seizure which include stigmatisation, social exclusion, disability, and increased risk of death.

Promoting long-term medicine taking is a complex task, involving combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, follow-up and supportive care. Individualised, patient-friendly treatment is an important first step and once daily regimens that are easy to swallow have been shown to improve outcomes, but no intervention will promote medicine taking in the absence of a supportive, concordant partnership between patients, carers and healthcare workers. ♦

REFERENCES

- Cramer JA, Glassman M, Rienzi V. *The relationship between poor medication compliance and seizures*. *Epilepsy & Behavior* 2002;3:338-42.
- Jones RM, Butler JA, Thomas VA, et al. *Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs*. *Seizure* 2006;15L504-8.
- U. Specht et al. *Postictal serum levels of antiepileptic drugs for detection of non-compliance*. *Epilepsy & Behavior* 4 (2003) 487-95.
- Davis KI et al. *Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population*. *Epilepsia*. 2005;49(3):446-54.
- Duncan JS. *The management of chronic epilepsy*. In: Sander JW, Walker MC, Smalles JE (Eds). *Epilepsy 2007: from cells to community*. A practical guide to epilepsy. International League Against Epilepsy (UK Chapter) and The National Society for Epilepsy. <http://www.e-epilepsy.org.uk/pages/articles/index.cfm> (accessed 26 June 2008).
- Hanna NH, Black M, Sander JW, et al. *Epilepsy – death in the shadows*. National sentinel clinical audit of epilepsy related deaths. London: HMSO 2002.
- Cockerell OC, Johnson AL, Sander JW, et al. *Mortality from epilepsy: results from a prospective population-based study*. *Lancet* 1994;344:918-21.
- Nilsson L, Farahmand BY, Persson PG, et al. *Risk factors for sudden unexpected death in epilepsy: a case-control study*. *Lancet* 1999;353:888-93.
- Faught E, Duh MS, Weiner JR, et al. *Nonadherence to antiepileptic drugs and increased mortality*. Findings from the RANSOM study. *Neurology* 2008, June 18 [epub ahead of print].
- Buck D, Jacoby A, Baker GA, Chadwick DW. *Factors influencing non-compliance with antiepileptic drug regimes*. *Seizure* 1997;6L87-93.
- Vergouwen AC, van Hout HP, Bakker A. *Methods to improve patient compliance in the use of antidepressants*. *Ned Tijdschr Geneesk*, 2002;146:204-7 (In Dutch).
- Carter S, Taylor D, Levenson R. *A question of choice – compliance in medicine taking*. A preliminary review (2nd edition). London: Medicines Partnership 2003.
- Kerr M. *Epilepsy and learning disability*. In: Sander JW, Walker MC, Smalles JE (Eds). *Epilepsy 2007: From Cell to Community, a Practical Guide to Epilepsy*. Eleventh edition. International League Against Epilepsy (UK Chapter) and the National Society for Epilepsy, London.
- WHO (World Health Organisation) (2003) *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organisation, Geneva.
- Clyne W, Granby T, Picton C. *A competency framework for shared decision making with patients*. *Achieving concordance in taking medicines*. Keele, Staffordshire: NPC Plus 2007.
- Morris, H. *Dysphagia, medicines and older people: the need for education*. *BRJ Community Nurs*. 2005;10:419-20.
- Wright, D. *Medication Administration in Nursing Homes*. *Nursing Standard*; 16:33-8.
- Strachan, I & Greener, M. *Medication related swallowing difficulties may be more common than we realise*. *Pharmacy in Practice*. 2005;411-4.
- Buelow JM, Johnson J. *Self management of epilepsy*. *Dis Manage Health Outcomes* 2000;8:327-36.
- Stokes T, Shaw EJ, Juarez-Garcia A, et al. *Clinical guidelines and evidence review for the epilepsies: diagnosis and management in adults and children in primary and secondary care*. London: Royal College of Physicians 2004.
- Cox K, Stevenson F, Britten N, Dunder Y. *A systematic review of communication between patients and health care professionals about medicine-taking and prescribing*. London: Medicines Partnership 2004.
- Smith T (2008) *A difficult pill to swallow? Improving outcomes in epilepsy using sodium valproate*. *British Journal of Neuroscience Nursing*, 2008;4(3):126-9.
- Herranz JL, Arteaga R, Adin J, Armijo JA. *Conventional and sustained-release valproate in children with newly diagnosed epilepsy: a randomized and crossover study comparing clinical effects, patients preference and pharmacokinetics*. *Eur J Clin Pharmacol* 2006;62:805-15.
- Stefan H. *Sustained release valproate in the treatment of epilepsy*. *Neuronews* 2006;6:1-8.

Focus on concordance in epilepsy

The
“patient friendly”
option

- ❖ Designed for concordance
- ❖ Once-a-day dose
- ❖ Simple evening dose
- ❖ Easy to swallow minitables
- ❖ High patient acceptability
- ❖ Concordance reduces seizure frequency

Episenta®
Prolonged Release Sodium Valproate

EPISENTA (Prolonged-Release Sodium Valproate)
ABBREVIATED PRESCRIBING INFORMATION

See Full SmPC For Details. Episenta 150 mg & 300mg capsules and Episenta 500 mg & 1000mg sachets contain prolonged release sodium valproate minitables. **Indication:** The treatment of all forms of epilepsy. **Dose:** Give in 1 - 2 single doses. **Monotherapy: Adults:** Start at 600mg daily increasing by 150-300mg at three day intervals to a max of 2500mg/day until control is achieved. **Children over 20kg:** Initial dosage - 300mg/day increasing to max. of 35 mg/kg bw/day until control is achieved. **Children under 20kg:** 20mg/kg bw/day; max. 40mg/kg/day. **Patients with renal insufficiency:** May require decreased dose. **Combined Therapy:** Dosage adjustments may be required. **Administration:** Swallow without chewing the prolonged-release minitables. **Contraindications:** Liver disease. Personal or family history of hepatic problems. Porphyrria. Hypersensitivity to valproate. **Precautions:** Suicidal ideation reported. The onset of an acute illness is an indication of the early stages of hepatic failure and requires immediate withdrawal of the drug. Routinely measure liver function in those at risk before and during the first six months of therapy. Discontinue if signs of liver damage occur or if serum amylase levels are elevated or if spontaneous bruising or bleeding occurs. Review patients who have issues with pancreatitis, renal insufficiency, SLE, hyperammonaemia, weight gain, diabetes or blood tests. Withdrawal of sodium valproate should be gradual. **Interactions, Pregnancy and Lactation:** See full SPC. **Undesirable Effects:** See full SPC. **Further information & MA Holder:** Beacon Pharmaceuticals Ltd. 85 High St., TN1 1YG UK. **Presentations & Price:** POM. Episenta 150 mg capsule x 100 PL 18157/0021, Episenta 300 mg capsule x 100 PL 18157/0022, Episenta 500 mg sachet x 100 PL 18157/0023 and Episenta 1000 mg sachet x 100 PL 18157/0024 have the following NHS prices: £5.70, £10.90, £18.00 & £35.50 respectively. **Date of text:** Oct 2008. Advert prepared Nov 08

Information about adverse event reporting can be found at
www.yellowcard.gov.uk
Adverse events should be reported to Beacon Tel: 01892-506958

Further information from Beacon
85 High St, Tunbridge Wells, TN1 1YG.
Tel: 01892 600930

 **Beacon**
PHARMACEUTICALS

Young People with Cerebral Palsy in Transition from Paediatric to Adult Health Services – Best Practice Recommendations



AMO Bakheit,

MD, PhD, FRCP,
Panel Chairman.

Correspondence to:

Magid Bakheit,
Professor of Neurological
Rehabilitation,
Mount Gould Hospital, Plymouth,
Devon PL4 7QD
Tel. +1752 434491
Email. magid.bakheit@
plymouth.nhs.uk

Appendix

PANEL MEMBERSHIP

Mr Simon Easton,
Occupational Therapist,
Walkergate Park International
Centre for Neurorehabilitation
and Neuropsychiatry,
Newcastle-upon-Tyne

Ms Karen Edwards,
Deputy Principal Physiotherapist,
Wood Street Health Centre,
Walthamstow

Ms Lesley Katchburian,
Clinical Specialist Physiotherapist
(Neurodisability) Great Ormond
Street Hospital, London

Dr Jean-Pierre Lin,
Consultant Paediatric Neurologist,
Evelina Children's Hospital,
London

Mr Mark Paterson,
Orthopaedic Surgeon, Royal
London Hospital, London

Mr Richard Parnell,
Head of Research and Public
Policy, Scope

Dr Valerie Shrubbs,
Community Paediatrician, Ashurst,
Southampton.

Cerebral palsy (CP) is the commonest cause of neurological disability in childhood and as many as 70% of children with CP survive into adult life.¹ Although the health and social care provision for these children is generally well organised and delivered by the paediatric services in the UK, there is a gap in the service provision of care for these individuals in their adolescent stage of development. This, and the need for the continuity of care, as well as the importance of the smooth transition from paediatric to adult services is now widely acknowledged.^{2,4}

Transfer from the care of the paediatric to the adult services is a major life event for young people with CP because of their unique and specific health, psychological, vocational and social needs. It requires close cooperation from the paediatric and adult medical teams in order to be seamless and successful.

This article aims to provide recommendations of best practice for achieving the transition of adolescents with CP from paediatric to adult care. The recommendations are based on published evidence and, where this is not available, on the clinical experiences of a panel of assembled experts (see appendix).

The policy context for transition from paediatric to adult services

The report 'Improving the life chances of disabled people'⁵ aims to promote planning and delivery of responsive, person-centred services, taking into account the needs and choices of individuals. It describes three key factors that are required for the effective support of young disabled people. These are:

- ▶ Planning for transition that focuses on the needs of the individual emphasising the role of the family and the need for it to be supported in a way that empowers disabled young people and their parents.
- ▶ Continuous service provision. It recom-

mends that the children and adult services should overlap to improve continuity of care.

- ▶ Access to more transparent and appropriate opportunities and choices.

Definition of transition

Transition, as defined by Blum et al.⁶ is 'the purposeful, planned movement of adolescents and young adults with chronic physical and mental conditions from child-centred to adult-orientated health care systems.' It is a process, not an event, and requires careful planning and timing.

Patient management in the paediatric and adult services differ greatly in their approach as to the issues of growth, development and involvement of the family. Consequently, a simple transfer to adult clinicians or allowing young people to 'drop out' of medical care is not acceptable and should be prevented.

Timing of transition

There is no 'right time' for transition and a flexible approach is crucial. Generally, the timing of transition should depend on the developmental readiness of the young adult as well as the capabilities of the adult providers.⁶ It has been suggested⁷ that transition should not occur until young adults have completed the developmental tasks of adolescence and have acquired the necessary skills and education to manage their condition largely independently of their parents.

Transfer of care from the paediatric to the adult service

The Panel (see Appendix) recommends that the transfer of care should be flexible and gradual and, ideally, coordinated by a community paediatrician. The process of transfer is best achieved through a joint transition clinic with members of both the adult and paediatric team which would see the young adult for up to two

Service provision	Minimum requirement	Ideal situation
Staff		
Training for the paediatric and adult medical teams in the management, care and transition of young people with cerebral palsy	✓	
Training of staff in disability diversity and communication skills	✓	
A 'key' person to be nominated e.g nurse, rehabilitation specialist, community paediatrician, to coordinate the transition from the paediatric to the adult service and be the intermediary for all medical and social needs	✓	
Specialist 'key' transition nurse or therapist in neurorehabilitation as part of both the paediatric and adult service		✓
Access to psychological support services – in paediatric liaison or community mental health		✓
Services		
Available information for young people with cerebral palsy, parents/carers regarding transition process	✓	
Good general information about treatment centres, available support services and resources	✓	
Dedicated out-patient room for young adults during clinic	–	✓
Young adult community services/out-patient services with resources tailored to their needs	✓	–
A national survey on the prevalence of cerebral palsy is required to enable better planning of services	✓	
Joint workings		
Integration and access to the key ancillary services e.g. social and therapy services and a further education advisor	✓	
Joint paediatric and adult CP transition clinics	✓	
Paediatric and adult neurorehabilitation services should be on the same hospital site		✓
Management of the young adult with CP should be based in the community. Services should be accessible in terms of location, access and service approach	✓	
Review of all equipment being used by the young person with CP prior to transfer to adult service, with a clear line of communication for future provision, repair and review	✓	

to three visits depending on their needs. Adequate and appropriate information on relevant health and social care and access to services should be provided to support young adults through the transition.

Summary of recommendations

The Panel felt that the following requirements (see Table) are necessary for a seamless transfer of care for the young adult. ♦

REFERENCES

1. Stevenson CL, Pharoah POD, Stevenson R. *Cerebral palsy – the transition from youth to adulthood*. Dev Med Child Neurol 1997;39:336-42.
2. White A, Forbes A, Ulman R et al. *Good practices that address continuity during transition from child to adult care: synthesis of the evidence*. Child Care Health Dev 2004;30:439-52.
3. Beresford B. *On the road to nowhere? Young disabled people and transition*. Child Care Health Dev 2004;30:581-7.
4. Department of Health. *Transition: Getting it right for young people. Improving the transition of young people with long term conditions from children's to adult health services*. London, DH, 2006.
5. Prime Minister's Strategy Unit. *Improving the life chances of disabled people. Final Report*. January 2005:125-53.
6. Blum R, Garell D, Hodgman C et al. *Transition from a child-centred to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine*. J Adolesc Health 1993;14:570-6.
7. Viner R. *Transition from paediatric to adult care. Bridging the gaps or passing the buck?* Arch Dis Child 1999;81:271-5.

The complete document is available from Louise Blakeborough, Chapter Five, T: +44 (0)1306 731800, M: 07831 444789, E: lblakeborough@chapterfive.co.uk.

The work leading to the production of 'Young People with Cerebral Palsy in Transition from Paediatric to Adult Health Services: Best Practice Recommendations' was supported by Scope and sponsored by Ipsen UK.



Registration is now open - for further information visit www.cp2009.com.au

Living with Dementia



Terry Pratchett, OBE

Terry Pratchett is one of the most popular authors writing today and is the acclaimed creator of the bestselling Discworld series. The first Discworld novel, *The Colour of Magic*, was published in 1985 and there are now 36 books in the series. The first Discworld novel for children, *The Amazing Maurice and his Educated Rodents*, was published in 2001 and was awarded the 2001 Carnegie Medal.

Long regarded as a significant satirist, Pratchett has won numerous literary awards, was appointed OBE in 1998 and has received four honorary doctorates.

Terry Pratchett featured in New Year Honours

Author Terry Pratchett was awarded a knighthood for services to literature in the New Year Honours list. The best-selling fantasy writer has sold almost 60 million books worldwide.

Neil Hunt, Chief Executive of Alzheimer's Society, says, "I would like to congratulate Terry on this fantastic and well-deserved achievement. Terry is not only a successful author and well-loved public figure; he is also playing a key role in fighting the misunderstanding and stigma surrounding dementia."

Seven hundred thousand people who have dementia in this country are not heard. I'm fortunate; I can be heard. Regrettably, it's amazing how people listen if you stand up in public and give away \$1million. This report goes some way to redressing that situation and allows others to tell you all about dementia. I regarded finding I had a form of Alzheimer's as an insult and I decided to do my best to marshal any kind of forces that I could against this wretched disease.

I have posterior cortical atrophy or PCA. They say, rather ingenuously, that if you have Alzheimer's it's the best form of Alzheimer's to have. This is a moot point, but what it does do, while gradually robbing you of memory, visual acuity and other things you didn't know you had until you miss them, is leave you more or less as fluent and coherent as you have always been.

I spoke to a fellow sufferer recently (or as I prefer to say 'a person who is thoroughly annoyed with the fact they have dementia') who talked in the tones of a university lecturer and in every respect was quite capable of taking part in an animated conversation. Nevertheless, he could not see the teacup in front of him. His eyes knew that the cup was there; his brain was not passing along the information. This disease slips you away a little bit at a time and lets you watch it happen.

When I look back now, I suspect there may be some truth in the speculation that dementia (of which Alzheimer's is the most common form) may be present in the body for quite some time before it is capable of diagnosis. For me, things came to a head in the late summer of 2007. My typing had been getting progressively worse and my spelling had become erratic. I grew to recognise what I came to call Clapham Junction days when the demands of the office just grew too much to deal with. I was initially diagnosed not with Alzheimer's but with an ischaemic change, a simple loss of brain cells due to normal ageing. That satisfied me until the next Clapham Junction day. I went back to my GP and said that I knew there was something more going on.

Fortunately, she knew well enough not to bother with the frankly pathetic MMSE test and sent me to Addenbrookes Hospital, Cambridge when, after examination of my MRI scan and an afternoon of complex testing, I was diagnosed with PCA – an uncommon variant which had escaped the eagle eyes of the original diagnostician.

When Milton's Satan stood in the pit of hell and raged at heaven, he was merely a trifle miffed compared to how I felt on that day. I felt totally alone with the world receding away from me in every direction and you could have used my anger to weld steel. Only my family and the fact I had fans in the medical profession, who were

able to give me useful advice got me through that moment. I feel very sorry for, and angry on behalf of, the people who don't have the easy ride I had. It is astonishing how long it takes some people to get diagnosed (they write to me). I cannot help but wonder if this is because doctors are sometimes reluctant to give the patient the stigma of dementia since there is no cure.

I was extremely fortunate in my GP. I think she was amazed to find that of the two specialists in my area, one had no experience of PCA and therefore did not feel he could not help me and the other would only take on patients over 65 – I was clearly too young to have Alzheimer's. I remember on that day of rage thinking that if I'd been diagnosed with cancer of any kind, at least there would have opened in front of me a trodden path. There would have been specialists, examinations, there would be in short, some machinery in place. I was not in the mood for a response that said, more or less, 'go away and come back in six years'.

My wife said 'thank goodness it isn't a brain tumour' but all I could think then was 'I know three people who have got better after having a brain tumour. I haven't heard of anyone who's got better from Alzheimer's'.

It was my typing and spelling that convinced me that the diagnosis was right. They had gone haywire. Other problems I put down to my looming 60th birthday. I thought no one else had noticed the fumbling with seat belts and the several attempts to get clothing on properly, but my wife and PA were worrying.

We still have the occasional Clapham Junction days, now understood and dealt with. I have written 47 novels in the past 25 years, but now I have to check even quite simple words – they just blank on me, at random. I would not dare to write this without the once despised checker, and you would have your work cut out to read it, believe me.

On the other hand – and this is very typical of PCA – when the kind lady who periodically checks me out asks me to name as many animals as I can, I started with the rock hyrax, the nearest living relative to the elephant, and thylacine – the probably extinct Tasmanian marsupial wolf. That's the gift or the curse of our little variant. We have extreme problems handling the physical world but we can come pretty close to talking our way out of it so you don't notice. We might have our shirts done up wrong, but might be able to convince you it's the new style.

I felt that all I had was a voice, and I should make it heard. It never occurred to me not to use it. I went on the net and told, well, everyone. I wish I could say it was an act of bravery. It wasn't and I find that suggestion very nearly obscene.

How brave is it to say that you have a disease that does not hint of a dissolute youth, riotous living or even terrible eating habits? Anyone can contract dementia; and every day and with a growing momentum, anybody does.

It occurred to me that at one point it was like I had two diseases – one was Alzheimer's and the other was knowing I had Alzheimer's. There were times when I thought I'd have been much happier not knowing, just accepting that I'd lost brain cells and one day they'd probably grow back or whatever. It is better to know, though, and better for it to be known, because it has got people talking, which I rather think was what I had in mind. The \$1million I pledged to the Alzheimer's Research Trust was just to make them talk a bit louder for a while.

It is a strange life, when you 'come out' people get embarrassed, lower their voices, get lost for words. Journalists, on the other hand – I appreciate that other people living with the disease don't get so much of this – find it hard to talk to me about anything else, and it dominates every interview: Yes, I said I had PCA ten months ago, yes, I still have it, yes, I wish I didn't, no, there is no cure. I can't really object to all this, but it strange that a disease that attracts so much attention, awe, fear and superstition is so under-funded in treatment and research.

We don't know what causes it, and as far as we know the only way to be sure of not developing it is to die young. Regular exercise and sensible eating habits are a good idea but they don't come with any guarantees. There is no cure. So we hope – more hope than would fit in Pandora's box, where it was the last thing.

We hope very carefully, that a half-way cure will arrive. Researchers are talking about the possibility of a whole palette of treatments or regimes to help those people with dementia to live active and satisfying lives with the dis-

ease kept in reasonably permanent check in very much the same way as treatments now exist for HIV. Not so much a cure therefore as – we hope – a permanent reprieve. We hope it will come quickly, and be affordable.

In the meantime we hope for Aricept, which is not a cure but acts as a line of sandbags against the rising tide of unknowing. However, it is available free only to those in the moderate stages of the disease: others must pay \$1,000 a year, which I do. Eligibility is determined by the MMSE test, and it would be so easy for a patient in the mild stage to cheat their score into the free zone that I take my hat off to those too proud or responsible to do so. I cough up. NICE says the change it makes at my stage is minimal, but we don't think so in our house, where those little changes make the difference between a dull day and a fine day. The disease is, after all about small changes, and it may be that individuals may indeed be individual.

And that is nearly it for hope at the moment. When my father was in his terminal year, I discussed death with him. I recall very clearly his relief that the cancer that was taking him was at least allowing him 'all his marbles'.

Dementia in its varied forms is not like cancer. Dad saw the cancer in his pancreas as an invader. But Alzheimer's is me, unwinding, losing trust in myself, a butt of my own jokes and on bad days capable of playing hunt the slipper by myself and losing. You can't battle it, you can't be a plucky 'survivor'. It just steals you from yourself.

And I'm 60; that's supposed to be the new 40. The baby boomers are getting older, and will stay older for longer – will expect to stay younger for longer. And they will run right into the dementia firing range. How will a society cope? Especially a society that can't so readily rely on those stable family relationships that traditionally provided the back-

bone of care in previous generations?

What is needed is will and determination. The first step is to talk openly about dementia because it's a fact, well enshrined in folklore, that if we are to kill the demon then first we have to say its name. Once we have recognised the demon, without secrecy or shame, we can find its weaknesses. Regrettably, one of the best swords for killing demons like this is made of gold – lots and lots of gold. These days we call it funding.

I believe that the D-day battle on Alzheimer's will be engaged quite shortly and a lot of things I've heard from experts in the field, not always formally, strengthen that belief. It is a physical disease, not some mystic curse; therefore it will fall to a physical cure. There's time to kill the demon before it grows.

I want to thank the Alzheimer's Society for publishing this report and bringing closer the day when the funding we need is made available. This report is part of the Society's Living With Dementia programme, which I'm pleased to see has the support of Comic Relief. A member of the Society once said at a conference: 'I am not dying of dementia – I am living with dementia'. And so the programme was born; to help those with dementia tell it like it is to the rest of the world and help influence for the better the lives of all of us with this 'embuggerance'. ♦

Terry Prachett's comments came at the launch of *Dementia - Out of the Shadows*, a new report into the impact stigma has on the lives of people with dementia.

The report and videos featuring four people with dementia sharing their views on stigma and diagnosis can be viewed at www.alzheimers.org.uk/outoftheshadows.



**INNOVATION IN EMG SYSTEMS
PEAKED IN THE 90'S.**

IT'S TIME FOR AN ADVANCE

Introducing the **ADVANCE™ NCS/EMG System**,
an innovation for your practice.
ADVANCE: Where comprehensive meets compact.
Visit emginnovation.com to learn more.
sales@electrodestore.co.uk

INNOVATION FROM
NEUROMetrix®
Neurotechnology Platforms to Transform Patient Care
+44 (0)1420 88688

Recent Advances in Glial Tumours



Dr Kathreena Kurian

qualified at Guy's and St Thomas' Hospitals, trained in neuropathology in Edinburgh and Cambridge and is currently working as a consultant at Addenbrooke's Hospital Cambridge, with part-time research at the Wellcome Trust Centre for Stem Cell Research, Cambridge. Her main research interest is in neurooncology with a special interest in glioma stem cell lines.

Correspondence to:

KM Kurian,
Wellcome Trust Centre for Stem Cell Research,
Tennis Court Road,
Cambridge CB2 1QR
Addenbrooke's Hospital,
Hills Road,
Cambridge CB2 0QQ, UK

Epidemiological data suggests that glioma incidence in adults is on the increase.¹ Why gliomas occur at all in the brain is still an interesting question - after all the brain is relatively protected from the environment by the blood brain barrier and is thought to have a very low proliferative potential compared with other organs. Recent advances in our understanding of gliomas revolve around the cancer stem cell theory and the cytogenetic and epigenetic control of these tumours. This article briefly outlines the general pathology of gliomas and describes these recent advances in the glioma field.

General pathology of gliomas

Primary CNS tumours are most often composed of cells that resemble glial cells, and are hence called gliomas. For example, tumours of various grades with cells resembling astrocytes, termed astrocytomas, are the most common glioma (See Figure 1 for examples of different grades of astrocytoma). The least aggressive of these tumours (grade I) are pilocytic astrocytomas with elongated processes and few mitotic figures, classically occurring in children. Grade II astrocytomas often

present in young adults with an average survival of five years after diagnosis and histologically comprise cells with bland nuclei and fibrillary processes. By contrast anaplastic astrocytomas (grade III) show obvious cellular atypia and mitotic activity and have a worse clinical prognosis. The most aggressive astrocytoma grade IV glioblastoma, is seen mainly in elderly adults and has a survival often measured in months. The other major categories of glioma include oligodendrogliomas and ependymomas, which display histological similarities to their putative glial origin.²

Cancer stem cell theory

The cancer stem cell was originally described in the field of haematological malignancies in acute myeloid leukaemia³ and has now been described in many solid tumours, including gliomas.^{4,5,6} By definition, cancer stem cells are a population of cells within a tumour that can divide infinitely and have the capacity to differentiate and therefore show similarities to 'normal' stem cells outwith the cancer field. These cancer stem cells are of great interest because they may represent the population of cells within a tumour that are resist-

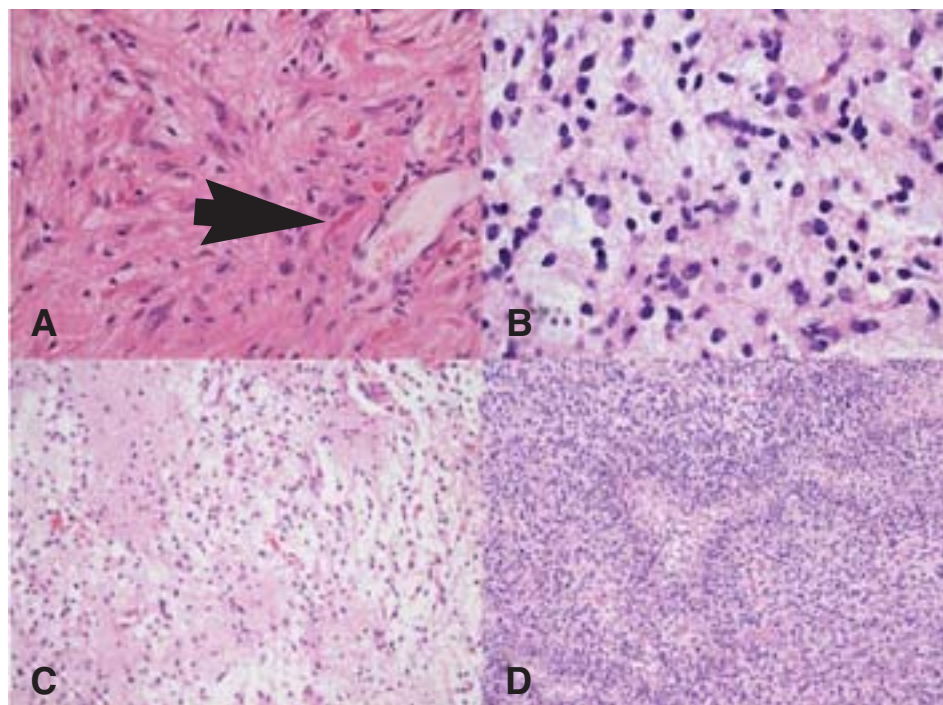


Figure 1: Astrocytic tumours stained with H&E.

A. (x20) Grade I Pilocytic astrocytoma showing elongated piloid cells and corkscrew eosinophilic Rosenthal fibres (arrow). B. (x 40) Grade II Diffuse astrocytoma showing bland nuclei with fibrillary processes. C. (x 40) Grade III Anaplastic astrocytoma with increasing pleomorphism and mitotic activity. D. (x10) Grade IV Glioblastoma with pseudopalisading of tumour cells around areas of necrosis.

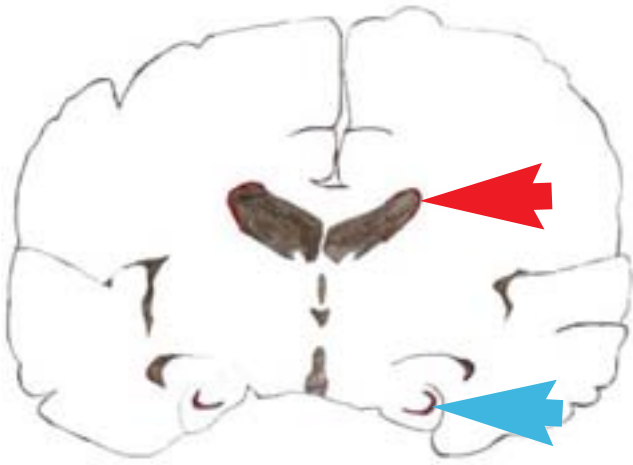


Figure 2: Putative adult neural stem cell niches: Subventricular Zone (red arrow) in the walls of the lateral ventricle and Dentate Fascia Subgranular Zone (blue arrow) of the Hippocampus. While cancer stem cells show in vitro similarities to neural stem cells, the cell of origin or tumour-initiating cell in adult gliomas remains unclear.

ant to therapy and responsible for tumour relapse. Whether cancer stem cells actually develop from pre-existing human neural stem cells or represent cells which have reacquired a stem-like state as a by-product of tumourigenesis or in vitro culture conditions remains controversial.^{4,5,6}

Normal human neural stem cells are thought to reside within the brain mostly in the subventricular zone lining the lateral ventricles and dentate gyrus of the hippocampus (see Figure 2).^{7,8} These stem cells persist throughout adulthood into old age and may divide symmetrically for self-renewal and asymmetrically to produce neurons, astrocytes and oligodendrocytes. Direct isolation of human neural stem cells from the human foetal brain using the cell surface marker CD133 by flow cytometry has been reported to produce human foetal brain cells that differentiate, persist and incorporate into the brain.⁷ The precise function of CD133, also known as prominin, remains unclear, however it was originally shown to be a haemopoietic stem cell marker.⁹ More recently the Dirks group and others have used CD133 to isolate a population of brain tumour stem cells within glioblastoma.¹⁰⁻¹⁴ Original papers suggested that CD133-positive stem-like cells were the only population of cells within the glioblastoma that were capable of producing tumours when transplanted into the brains of immunodeficient mice.¹³ More recent studies suggest that this may not always be the case.¹⁴

...the ability to control glioma cells by forcing them to undergo a differentiation programme represents a major conceptual advance in the field

The question whether there is a universal glioma cancer stem cell, or whether different subtypes of glioma contain different stem cells remains unanswered. Work by Gilbertson's group suggests that the stem cell may vary according to the nature of the original tumour. He has shown that subtypes of a different type of glial tumour (ependymoma) may derive from radial glia at different locations at different stages of development in the nervous system. It is possible that radial glia may represent the stem cell of ependymomas. These cells express CD133, RC2 and nestin, which are present on radial glia and human neural stem cells.¹⁵

It seems that glioma stem cells are dependent on their microenviron-

ment in order to maintain stem cell properties. There is evidence to suggest that endothelial cells interact and secrete factors in vitro that maintain cells in a stem-like state.¹⁶ Increasing the number of endothelial cells expands the population of self-renewing cells and their tumourigenic properties. It is therefore possible that stem-like-cells survive within a vascular niche.

Recent exciting work has shown that in vitro it is possible to make certain types of glioma initiating stem cells differentiate into neuronal type cells using manipulation of the Bone Morphogenetic Protein (BMP) pathway, which is involved in differentiation of human embryonic stem cells to human neural stem cells.¹⁷ This study demonstrates a major differentiation block in a subset of glioblastoma caused by the Polycomb repressor complex (PRC)-mediated epigenetic silencing of the BMP1B promoter, analogous to early embryonic neural stem cells. Although this is a radical departure from traditional therapy using surgery, chemo- and radiotherapy, the ability to control glioma cells by forcing them to undergo a differentiation programme represents a major conceptual advance in the field.

Cytogenetics and epigenetics of glioma

The most recent major advance in our understanding of glioblastoma has been achieved by the Cancer Genome Atlas (TCGA) pilot project. This aims to assess the value of large-scale multidimensional analysis of molecular characteristics in human cancer and to provide data rapidly to the research community. They recently reported the interim integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas.¹⁸ They studied alterations in the RTK/RAS/PIK pathway, and p53 and RB signalling pathways, involved in the control of cell cycle and apoptosis in the majority of glioblastomas. RTK/Ras/PIK signalling was altered in 88%, p53 signalling altered in 87% and RB signalling altered in 78% of cases. This study appears to blow apart the conventional dogma that primary and secondary gliomas derive by different restricted genetic pathways. It implicates different players in glioblastoma pathogenesis including ERBB2, NF1 and PIK3R1, which are different components of growth factor and cell cycle control pathways (See Table 1). This study also examined the methylation status of MGMT, a repair protein that specifically removes promutagenic alkyl groups from DNA. This has been implicated in drug resistance since it reduces the cytotoxicity of alkylating agents such as temozolomide - an alkylating agent used to treat glioblastoma. Patients with newly diagnosed glioblastomas with MGMT methylation respond well to temozolomide. The alkylated DNA results in cycles of futile mismatch repair, leading to cell death. The study

showed that treated glioblastomas were under a strong selective pressure to lose mismatch repair function predicting that such patients would eventually develop treatment resistance. The authors suggest that combining alkylating agents with an agent designed to target mismatch-repair-deficient cells as a first-line therapy may minimise the emergence of drug resistance.¹⁸

There has been recent progress in gliomas traditionally thought to lack karyotypic abnormalities. Such genetic abnormalities may be key events in the development of these tumours. In particular a tandem repeat has been identified in most pilocytic astrocytomas which produces a novel

oncogenic BRAF fusion gene, involved in growth factor stimulated tyrosine kinase pathways which transforms fibroblasts in vitro.¹⁹ A different type of glioma (subependymoma) also carries cytogenetic abnormalities in a proportion of cases.²⁰ As the sensitivity of these techniques increases and we head inexorably

to whole genome sequencing of tumours, the number of abnormalities identified will further increase.

Conclusions

The cancer stem cell theory predicts that not all tumour cells are equal. We may have the

ability to control glioma cells by forcing them to differentiate. This represents a major conceptual advance in the field, but it is still controversial. Major new insights into the genetics and epigenetics of gliomas will hopefully direct a new era of patient-specific combined molecular therapies. ♦

Table 1: Glossary showing a selection of putative candidates and pathways involved in gliomagenesis

Candidate Molecule	Function of Pathway
CD133 (prominin 1/PROM1)	Transmembrane molecule, function still unclear, expressed on haemopoietic neural stem cells. First used to isolate brain tumour stem cells from glioblastoma. Found in a range of tumour types.
RC2	Marker of radial glia (the progenitor of glial and neuronal lineages). Expressed on the putative ependymoma stem cell.
Nestin	Intermediate filament expressed in developing CNS, PNS and myogenesis. Upregulated in some pathological states, a putative marker of ependymoma stem cells and expressed in glioblastoma and other tumour types.
BMP (Bone Morphogenetic Protein)	Member of the Transforming Growth Factor Beta family of secreted ligands. Originally described in bone formation, but has pleotropic effects on the developing nervous system. BMPs have differing effects on glioma stem cells including promoting differentiation in certain tumour lines.
RTK/Ras/PIK	Receptor tyrosine kinases (RTKs) are cell surface receptors for many polypeptide growth factors, cytokines and hormones eg Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF). Receptor tyrosine kinases are key regulators of normal cellular processes and have a critical role in the development and progression of many types of cancer via Ras, PIK and other modulators.
p53	('guardian of the genome') The transcription factor encoded by the TP53 gene. p53 regulates the cell cycle and thus functions as a tumour suppressor that is involved in preventing many cancers including gliomas.
RB	Retinoblastoma protein is involved in cell cycle control and is a well known tumour suppressor gene involved in the formation of certain gliomas.
ErbB2	Member of Epidermal Growth Factor Receptor Tyrosine Kinase family (see above Receptor Tyrosine Kinases).
NF1	(neurofibromin), an intracellular cell signal molecule. A negative regulator of the Ras oncogene and implicated in tumourigenesis outwith the neurofibromatosis type 1 syndrome, including in glioblastomas.
PIK	Phosphoinositide kinases- family of related enzymes that phosphorylate phosphoinositide lipids generating lipid second messengers involved in cell growth, differentiation, survival, proliferation and migration.
MGMT	Repair protein that specifically removes promutagenic alkyl groups in DNA. Implicated in drug resistance since it reduces the cytotoxicity of alkylating agents.
Ras, BRAF	Part of a signal transduction pathway that regulates cell growth, elevated in approximately 30% of human cancers. RAS is mutated in approximately 15% of human cancers.
RAF	There are three RAF proteins, A-RAF, B-RAF and C-RAF. Many different types of B-RAF mutations have been found in human cancers. Activating mutations stimulate proliferation of cells and protect them from apoptosis. B-RAF has recently been implicated in the formation of pilocytic astrocytomas.

REFERENCES

- Hess KR, Boglio KR, Bondy ML. *Adult glioma incidence trends in the United States*. Cancer 1997;2000;101(10):2293-9.
- Kleihues P, Cavenee WK. *WHO Classification of Tumours of the Nervous System 2007*.
- Bonnet D and Dick JE. *Human acute myeloid leukaemia is organized as a hierarchy that originates from a primitive hematopoietic stem cell*. Nat Med 1997;3:730-7.
- Stiles CD, Rowitch DH. *Glioma stem cells: A Midterm Exam*. Neuron 2008;58:832-46.
- Reya T, Morrison SJ, Clarke MF and Weissman IL. *Stem cells, cancer, and cancer stem cells*. Nature 2001;414:105-11.
- Tan BT, Park CY, Ailles LE, Weissman IL. *The cancer stem cell hypothesis: a work in progress*. Lab Invest 2006;86:1203-7.
- McKay R. *Stem cells in the central nervous system*. Science 1997;276:66-71.
- Pollard SM, Conti L, Sun Y, Goffredo D, Smith A. *Adherent neural stem (NS) cells from fetal and adult forebrain*. Cereb Cortex 2006;16:112-20.
- Uchida N, Buck DW, He D et al. *Direct isolation of human central nervous system stem cells*. PNAS 2000;14720-5.
- Ignatova TN, Kukekov VG, Laywell ED et al. *Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers in vitro*. Glia 2002;39:193-206.
- Galli R, Binda E, Orfanelli U, et al. *Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma*. Cancer Res 2004;64:7011-21.
- Hemmati HD, Nakano I, Lazareff JA, et al. *Cancerous stem cells can arise from paediatric brain tumor*. Proc. Natl. Acad. Sci. USA 2003;100:15178-83.
- Singh SK, Clarke ID, Teraski M, et al. *Identification of a cancer stem cell in human brain tumours*. Cancer Research 2003;63:5821-8.
- Joo KM, Kim SY, Jin X, et al. *Clinical and biological implication of CD133-positive and CD133-negative cells in glioblastomas*. Lab Invest 2008;88:808-15.
- Taylor MD, Poppleton H, Fuller C et al. *Radial glia cells are candidate stem cells of ependymoma*. Cancer Cell 2005;8:323-35.
- Gilberston R. *Rich Making a tumour's bed: glioblastoma stem cells and the vascular niche*. Nat Rev Cancer. 2007 Oct;7(10):733-6.
- Nakano I, Saigusa K, and Kornblum HI. *BMPing Off Glioma Stem cells*. Cancer Cell 2008;13(1):3-4.
- Cancer Genome Atlas Research Network. *Comprehensive genomic characterization defines human glioblastoma genes and core pathways*. Nature 2008;455(7216):1061-8.
- Jones DTW, Kocialkowski S, Liu L et al. *Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas*. 2008 Cancer Res/*; In Press.*
- Kurian KM, Jones DTW, Marsden F et al. *Genome-wide analysis of subependymomas shows underlying chromosomal copy number involving chromosomes 6, 7, 8 and 14 in a proportion of cases*. Brain pathol 2008;469-73.

Neurological literature: Headache (Part 5)



Dr 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.

Correspondence to:

Dr Andrew Larner,
Walton Centre for Neurology
and Neurosurgery,
Lower Lane, Fazakerley,
Liverpool, L9 7LJ, UK.
E. a.larner@thewaltoncentre.nhs.uk

Previous articles in this series¹⁻⁴ have focused on literary descriptions of headache. As in clinical practice, it is now finally time for headache description (relatively easy) to give way to headache treatment (very difficult), specifically literary accounts of therapy for headache. The magnitude of the problem before us is perhaps no better illustrated than by the fact that many great and able individuals have suffered from headache without having specific solutions to their problem. Among famous migraineurs one may note characters as diverse as John Hughlings Jackson (the “father of English neurology”)⁵ and, possibly, Harry Potter.⁶

Some possible therapies have been mentioned in previous articles: leeches and dental extractions in Jane Austen's *Sanditon*,¹ eye glasses in LM Montgomery's *Anne of Green Gables*,¹ a kiss in Robert Herrick's poem *The Head-ake*,² praying to saints or fasting,³ and using a leaf and charm by Socrates in Plato's *Charmides*.⁴ (The use of the guillotine, reported by Dickens as an effective headache cure,³ may be discounted because of the invariably unfavourable adverse effect profile.) A further possible example of charms may be the glass balls sold for headaches by Melquiades and his tribe of gypsies to the villagers of Macondo in *One hundred years of solitude* by Gabriel Garcia Marquez. Four generations later in the same village, the adolescent Meme drinks cane liquor with her girl friends, then wakes at midnight with “her head splitting with pain and drowning in vomited gall”: migraine? Her mother, Fernanda, gives her a vial of castor oil (a purgative), puts compresses on her stomach and ice cubes on her head.⁷ Progress!

Other plant products have been recorded as therapeutic for headache. The herb skullcap, which was thought to bear an affinity to the shape of a skull, was once used as a cure for headache,⁸ evidently an example of the theory of signatures. Tobacco was apparently a treatment for migraine, amongst other ailments, in Shakespeare's London.⁹ Not all plants however are beneficial: OED lists “head-ache” as a rustic name used in the nineteenth century for the wild poppy *Papaver Rhoeas*, since “any one by smelling it for a very short time may convince himself of the propriety of the name”. In *What Katy Did* (1872), camphor is suggested for Katy's friend Imogen when she has a headache, and likewise for Aunt Izzie, but the latter turns out to have typhoid fever from which she succumbs.

Thomas Mann's novel *Doctor Faustus* (1947) has been noted to contain accounts of several neurological disorders, including neurosyphilis, meningitis, and stroke, as well as migraine.^{10,11} For the latter, the landlady Frau Schweigstill suggests that the victim, Adrian Leverkühn, take “real strong tea, made real sour with lots of lemon”. (It is not clear whether Mann himself suffered headaches: his autobiographically inspired work Tonio Kroger published in his late twenties [1903] contains no reference.) The efficacy of this (folkloric?) remedy is not recorded, but in Jane Austen's *Mansfield Park* (1814) Fanny Price's headache, one of several instances in which this author mentions headache,¹² improves after drinking tea prepared by her sister Susan, though it may be the “well-timed kindness” rather than caffeine which induces this effect. The efficacy of strong tea in migraine has been emphasized by some authors,¹³ whilst others insist on the withdrawal of all tea, as a source of caffeine, itself an analgesic, particularly in chronic migraine. Might the presence or absence of milk be the cause of such diametrically opposed medical advice? “It is a bad thing to give milk to persons having headache” according to Hippocrates (*Aphorisms*, 64), but equally he advises elsewhere that “abstinence is bad in headache” (*Regimen in acute disease*, 8).

Abstinence from what, we wonder? Could the father of medicine have meant sex, perhaps? No less an authority than John F Kennedy (1917-1963) is said to have stated, in conversation with Harold Macmillan in Bermuda in 1961, that “If I don't have a woman for three days, I get terrible headaches” (http://en.wikiquote.org/wiki/John_F_Kennedy, accessed 02/09/08). If this were an efficacious form of prophylaxis, one can imagine that many headache patients might be enthusiastic about giving it a try, although of course headache itself may be a consequence (primary headache associated with sexual activity). What about drugs and alcohol? The nineteenth century clergyman Francis Kilvert who suffered from headache and face ache which may have been cluster headache^{3,14} reported in his diary trying “laudanum and port wine, but nothing did any good”, although on a later occasion he found that “After dinner and four glasses of port I felt better”.

Returning to the theme of headache treatment recommended by doctors, rather than laymen, one might consider the case of Roald Dahl. Recovering in Alexandria after a war-time plane crash (he was at that time a fighter pilot in the

RAF) which caused head injuries, Dahl had "such terrific headaches" that he had to lie flat for seven days in darkness doing nothing, followed by a new treatment regime: "... they are going to give me intravenous [sic] saline and pituitary [sic] injections & make me drink gallons of water – its another stunt to get rid of the headaches." Might he have had low pressure headache? The efficacy of this measure is not recorded, but Dahl did return to active service, only to be invalided out later because of "blinding headaches ... when I was flying ... doing very steep turns and making sudden changes of direction."¹⁵

William Heberden (1710-1801) was one of the most noted physicians of his day, remembered not only for Heberden's nodes but also for one of the first clear descriptions of angina, although he was not aware of its cardiac origin, a discovery ascribed to Edward Jenner. Heberden's approach to headache may be surmised from the correspondence of one of his notable patients, the potter Josiah Wedgwood (1730-1795). Between 1788 and 1790 Wedgwood told correspondents of his "nervous or rheumatic headache" which one physician had ascribed to gout. In 1788, Heberden prescribed for him a "blister", which apparently proved partially successful, and advised a holiday.¹⁶

The risks of medication in the genesis of headache are, perhaps unwittingly, alluded to by Anthony Horowitz,¹⁷ who says of an accident-prone character in *The blurred man* that "He bought headache pills that actually gave you a headache ...". The possibility of medication (aspirin) over-use headache in a patient labelled, implausibly to my diagnostic eye, as having "vascular dementia" in Ian McEwan's *Atonement* has been previously noted.² ♦

The herb skullcap, which was thought to bear an affinity to the shape of a skull, was once used as a cure for headache, evidently an example of the theory of signatures

REFERENCES

- Larner AJ. "Neurological literature": headache. *Advances in Clinical Neuroscience & Rehabilitation* 2006;5(6):23-24.
- Larner AJ. "Neurological literature": headache (part 2). *Advances in Clinical Neuroscience & Rehabilitation* 2006;6(2):37-38.
- Larner AJ. "Neurological literature": headache (part 3). *Advances in Clinical Neuroscience & Rehabilitation* 2007;7(1):27-28.
- Larner AJ. "Neurological literature": headache (part 4). *Advances in Clinical Neuroscience & Rehabilitation* 2008;7(6):17.
- Critchley M, Critchley EA. *John Hughlings Jackson. Father of English neurology*. New York: Oxford University Press, 1998: 192.
- Sheftell F, Steiner TJ, Thomas H. *Harry Potter and the curse of headache*. *Headache* 2007;47:911-916.
- García Marquez G. *One hundred years of solitude*. London: Picador, 1978 [1967]: 15;221,222.
- Richardson R. *Death, dissection, and the destitute*. London: Routledge & Kegan Paul, 1987: 301 n73.
- Bryson B. *Shakespeare. The world as a stage*. London: Harper, 2007:54-5.
- Kierulff H. *Neurology in Thomas Mann's novels*. *Acta Neurol Scand* 2003;107:430.
- Rot U. *Thomas Mann: neurological cases from Doctor Faustus*. *Pract Neurol* 2004;4:180-183.
- Larner AJ. "A transcript of actual life": headache in the novels of Jane Austen. *Headache* 2008;48:(in press).
- Sacks O. *Migraine (Revised and expanded)*. London: Picador, 1992: 241,253,254.
- Larner AJ. *Francis Kilvert (1840-1879): an early self-report of cluster headache?* *Cephalalgia* 2008;28:763-766.
- Dahl R. *Going solo*. London: Puffin, 2001 [1986]: 116,202.
- Finer A, Savage G (eds.). *The selected letters of Josiah Wedgwood*. London: Cory, Adams & Mackay, 1965: 309,311,312,321-322.
- Horowitz A. *The blurred man*. London: Walker Books, 2002: 61.



UCL

UCL INSTITUTE OF NEUROLOGY

in association with the

National Hospital for Neurology
and Neurosurgery,
Queen Square, London WC1

Queen Square Advanced Short Courses

11th-15th May 2009

Epilepsy	(11 May)
Neurogenetics	(12 May)
Movement Disorders	(13 May)
Movement Disorders	(14 May - morning only)
Neurosurgery	(14 May - afternoon only)
Neuroinflammation	(15 May)

Course fees

£750 for the whole week

£220 per day

£185 per day for clinical trainees

£150 per day student rate.

(to include refreshments and lunch)

For further details please contact:

The Education Unit

UCL Institute of Neurology

National Hospital for

Neurology and Neurosurgery

Queen Square, London WC1N 3BG

Tel: 020 7692 2346 Fax: 020 7692 2345

Email: J.Reynolds@ion.ucl.ac.uk

www.ion.ucl.ac.uk

*The UCL Institute of Neurology promotes
teaching and research of the highest quality in
neurology and the neurosciences*

Key Research Event
MS Frontiers

21-22 May 2009
Sofitel
London

For further info please email: conferenceadmin@mssociety.org.uk

Primary Care Neurology Society Meeting

Conference details: 6 November, 2008; Cardiff, UK. **Reviewed by:** CAH Fisher, The Marches Surgery, Leominster, UK. AJ Larner, WCNN, Liverpool, UK.

The recent meeting of the Primary Care Neurology Society (P-CNS; www.p-cns.org.uk), which seeks to develop links between primary and secondary care in order to optimise the care and management of patients with neurological disorders, covered a wide variety of subjects in lectures, debate, and 'breakout sessions'.

Pain is a big part of GP life. Professor Joanna Zakrzewska ("Pro-Zak") gave a comprehensive overview of facial pain and its management, reporting a prevalence of 12–15% and stressing the importance of differentiating dentoalveolar, neuropathic, oral and other pain, since this determines the appropriate referral pathway. She focused specifically on four conditions and the terms that patients often use to describe their pain: temporomandibular joint dysfunction is often 'dull and nagging', burning mouth syndrome (BMS) is 'burning and tingling', persistent idiopathic facial pain is often 'nagging' and trigeminal neuralgia (TN) is 'sharp and shooting' and sometimes likened to electric shocks. Patients often have other pain syndromes, such as irritable bowel syndrome, and 'hypervigilance' for physical symptoms is common. Patient reassurance and education, for example with leaflets, were common themes in the management of all these conditions, along with identification of comorbidity such as depression which may merit treatment in its own right. As for pharmacotherapy, though often used (e.g. tricyclics, SSRIs) there is little compelling evidence in terms of randomised controlled trials, the best available being for carbamazepine and oxcarbazepine in TN (guidelines are available, e.g. *European Journal of Neurology* 2008;15:1013-28) and clonazepam in BMS. Cognitive behaviour therapy is an option, although access is limited.

Also on the subject of pain, Mark Ritchie spoke on chronic non-malignant pain. A useful overview of 'yellow flags' included strategies for combating commonly held misbeliefs such as that all pain must resolve before resuming work or activities, and that pain is harmful, which leads to fear avoidance behaviour. The use of pain diaries was promoted, requiring patients to score their pain daily, and list one positive and one negative experience each day, thereby encouraging linkage between psychological state and pain experience. Diaries can also allow patients to avoid displaying pain behaviour ('catastrophising') at doctor consultations, by referring to pain levels over a period of time.



Venue: Welsh Institute of Sport, Cardiff.

Dementia and mild cognitive impairment (MCI) were addressed by Roy Jones. His advice regarding the general assessment of patients with memory complaints in primary care was: history taking, including from a reliable informant, especially focusing on medication use (anticholinergic drug effects are an important cause of non-degenerative MCI) and alcohol consumption; clinical examination; and then investigations. Treatment of a low vitamin B12 level in these patients was generally found to produce no change at all. As regards cognitive tests, MMSE was advocated if GPs were comfortable with this, although it has

A sea change in GP attitudes to stroke may be one necessity if thrombolytic therapy is to become a reality

been thought too long for use in the primary care setting and interpretation is difficult. A recent paper suggested that other screening tests such as GPCog and MiniCog might be helpful in primary care (*International Psychogeriatrics* 2008;20:911-26).

A lively debate on the role of placebo as an active treatment for neurological conditions resulted in a change of mind in favour for a few delegates about the acceptability of this approach. Edzard Ernst argued that since the placebo effect is part of the non-specific effect of all medications, in addition to the desired pharmacological effect, the placebo effect is a bonus which negates the point of prescribing a placebo on its own. However, as Andrew Lawson made clear, the ethical debate is far

from simple, and no doubt will continue to run.

Breakout sessions examined stroke and TIA, MS relapse, anxiety and depression, and movement disorders. Since 40% of strokes are recurrent events, Hamsaraj Shetty pointed out that opportunities for intervention are being missed. In a comprehensive talk, he covered the evidence base for thrombolysis, which, though compelling, is currently available in only two centres in Wales, and not on a full-time basis. A sea change in GP attitudes to stroke may be one necessity if thrombolytic therapy is to become a reality, with patients being directed immediately to hospital, rather than seeing the GP first. John Potakar covered the classification of anxiety disorders and their differentiation from normal anxiety, and the potential role of alcohol, an anxiolytic, in sustaining anxiety through a dependence syndrome. Delegates were challenged by a case scenario which encompassed the pharmacodynamics and pharmacokinetics of SSRIs, the discontinuation syndrome, and the serotonin syndrome. Dwarak Sastry and his specialist Parkinson's disease nurse gave a comprehensive overview of diagnosis and treatment of PD, particularly stressing non-organic symptoms. Anxiety is present in 20-40% of patients, and often fluctuates with the motor state. Treatment should therefore be targeted at improving motor fluctuations, and at treating depression.

Alistair Church rounded off the day with an exposition on the causes and treatment of dizziness, a topic often perceived as complex but from which a few simple lessons may be distilled. His clinical algorithm, eminently applicable in primary care, required initial differentiation of vertigo from other causes of dizziness, then of first episode from recurrent vertigo. The former may be vestibular neuronitis or an acute brainstem event: a lack of neurological signs, a build up of symptoms, patient ability to stand, and a positive head thrust test favour vestibular neuronitis. For recurrent vertigo, the key question relates to whether the symptoms are positional or not. Non-positional recurrent vertigo may be migrainous vertigo, a condition far commoner than Meniere's disease. Recurrent positional vertigo suggests the diagnosis of benign positional paroxysmal vertigo which may be diagnosed with the Dix-Hallpike test and treated with the Epley manoeuvre, both of which may, with a little training, be performed in the primary care setting. ♦

Progress: Advancing Parkinson's Research

The Parkinson's Disease Society research conference

Conference details: 3-4 November, 2008; York, UK. **Reviewed by:** Neil Archibald, Parkinson's Disease Society Research Fellow, Clinical Ageing Research Unit, Newcastle University, UK.

Neurology, with all its sub-speciality interests, is well served by the dazzling array of conferences that pepper almost every month of the year. In the era of the 'mega-conference', with thousands of delegates, satellite symposia and parallel sessions, one could be forgiven for overlooking the arrival of a new kid on the block. That would be a shame however as the recent Parkinson's Disease Society (PDS) conference in York brings something a little different to the table. With a focus on showcasing the work of young researchers, many supported or funded by the PDS, alongside that of keynote speakers from around the world, there was a relaxed and almost 'family' feel to the two-day meeting.

After a welcome from the Director of Research and Development of the PDS, the conference kicked off in earnest with Bastiaan Bloem's entertaining and fascinating tour of gait and balance disturbances in Parkinson's disease (PD) and related disorders. With a focus on clinical assessment of gait disorders, why and how people with PD fall, the neural correlates of gait and the development and delivery of cost-effective community physiotherapy in PD, the tone was set for a meeting marrying both basic science and clinical approaches to movement disorders in the hope of translating research into new pharmacological and non-pharmacological treatment options for PD.

The second keynote speaker, Jeffrey Kordower, outlined the state-of-the-art in stem cell and gene therapy research, both in non-human primate models of PD and, most importantly, the early trial results in humans. After the disappointment of the 'false dawn' of foetal transplants for PD treatment, the speaker introduced a necessary note of caution in the interpretation of results from non-blinded non-placebo controlled surgical trials in the field. Despite the media interest, it seems stem cell therapy is a long way from the bedside or neurosurgical theatre but the pace of progress in gene therapy research is brisker. Safe and tolerable it may be in the small number of selected patients so far to receive the treatment but we must wait patiently for the larger-scale trial results before loosening the grip on the reins of our enthusiasm for another surgical breakthrough in the treatment of PD.



York Minster.

The last of the keynote speakers, Olivier Rascol, provided an insightful tour-de-force of pharmacological 'symptomatic' treatments for PD. Alas, we seem as far as ever from neuroprotection, so long the 'holy grail' for patients and clinicians alike. The pharmacological armoury is swelling however, with long-acting dopamine agonists and partial agonists, transdermal patches and drugs with non-dopaminergic mechanisms of action. Which of the dizzying array of cholinesterase inhibitors, adenosine A2 antagonists, serotonergic agonists and antagonists and noradrenergic antagonists will find a niche in clinical practice will depend on high-quality trials, but both surgical and pharmacological treatment options are evolving steadily and, importantly, offer something to both patients, carers, researchers and doctors alike – hope.

On to the flurry of short platform sessions now where I must declare an immediate conflict of interest. Setting aside my own (literally) fifteen minutes of 'fame', I was struck by the broad canvas of the meeting and the enthusiasm communicated by all those presenting their research – many for the first time. We learned of the influence of the tau genotype on dementia susceptibility in Parkinson's disease and how our current pathological staging systems leave many questions on the role of α -synuclein unanswered. The fascinating finding, in a large autopsy sample, of widespread α -synuclein pathology in many patients without clinical

signs of dementia or extrapyramidal symptoms heightens the ongoing debate as to the precise role Lewy bodies and Lewy neurites play in the development of PD and DLB.

We were introduced to the rat model of levodopa-induced dyskinesia with thoughts on the aetiological factors involved and the potential use of topiramate in its management – at least in rats! We also learned that dyskinetic rats find that unfamiliar surroundings worsen their dyskinesias whilst their favourite coloured sawdust in a familiar cage reduced the abnormal movements. Sawdust on the movement disorder clinic floor – a move unlikely to curry favour with infection control gurus in the NHS but a fascinating thought nonetheless.

The preliminary results of the PD-SURG trial were also presented, demonstrating a benefit in quality of life and motor function compared to best medical management for those undergoing deep brain stimulation (DBS). This confirms the bedside experience of most involved in referring patients for DBS, although the problem of identifying the candidates most likely to benefit remains a difficult issue. Early results from the PROMS-PD study, examining mood disturbances in PD, were also covered. We are only now beginning to appreciate the impact of depression and anxiety on people with PD and this important study should help us discern the clinical phenotypes of mood disorders in PD and throw light on the best treatment options for those affected.

As ever, one of the highlights of the meeting was the poster sessions, with an opportunity to chat with researchers on a more informal footing. I was struck not only by the high quality of the research but also by the breadth of projects on show. It would appear that almost no animal species is safe from our attempts to model the genetic, cellular and environmental factors that might contribute to the development of PD. In addition to the standard mice and rat models I was particularly interested to see the growth in research using the very accessible central nervous systems of *Drosophila*, zebrafish and nematodes. In the pharmacology collection, the focus seemed to be on the search for novel neuroprotective agents to prevent the striatonigral loss instigated by neuronal insults such as

MPTP. In the absence of methods to promote parkinsonism in animals mimicking the chronic decline of human PD the use of such agents remains a necessity.

I was heartened to see a clinico-pathological study from London suggesting that our clinical acumen does yield accurate diagnoses of PD and related disorders, at least in those patients attending specialist movement disorder services. Non-motor symptoms such as dementia, visual hallucinations and anxiety as well as orthostatic hypotension also seem highly characteristic of pathologically proven PD cases. I was also interested to read work from Northumbria NHS Trust on the

prevalence and nature of urinary symptoms in PD – a seemingly ubiquitous problem in PD and worthy of a much higher profile than it usually receives.

Those able to stay for the conference conclusion were fortunate to witness the prize giving ceremony for the two best posters. The honours went jointly to two groups of researchers; one from the University of Manchester and one including contributions from Northumbria, Newcastle, Glasgow and Belgium. The former received the award for their work on changes in the expression of G-protein signalling in the striatum of a unilateral model of PD and levodopa-induced dyski-

nesia and the latter for their studies on optimal cognitive and auditory cueing strategies for gait problems in PD. The prize originates from the generosity of the family of Dennis Pooley, who struggled with Parkinson's and Lewy body dementia until his untimely death. I can think of no better memorial to his life nor a more inspiring reminder of why it is that we had all been gathered under the same roof for the previous two days. My only worry for next year's conference is that the organisers might need to find a bigger venue, as a quick straw poll suggested most attendees had found the meeting as enjoyable as I and would hope to return. See you there in 2009? ♦

19th Meeting of the European Neurological Society

Conference details: 20-24 June, 2009; Milan, Italy. **Report by:** Prof G Said, ENS Executive Committee.

PREVIEW

Teaching programme:

- 22 practical workshops
- Practical sessions in clinical neurophysiology
- 23 Teaching courses covering all important topics in Neurology

Early registration deadline:

22 April, 2009

Abstract submission deadline:

11 February, 2009



programme for neurologists in training many young neurologists can be invited to attend high quality teaching and scientific sessions.

The teaching programme will continue on Sunday morning and afternoon with courses covering the different neurological subspecialties ranging from neuromuscular disorders to movement disorders and current treatments in neurology. An important workshop will be devoted to the management of multiple sclerosis (MS) patients which includes administration of disease-modifying treatment, symptomatic relief and neurorehabilitation. Many MS patients suffer from frequently severe and disabling symptoms, that affect their quality of life. Management of these symptoms is an important part of MS therapy. These symptoms include loss of mobility, spasticity, tremor, abnormal eye movements, pain, paroxysmal symptoms, bladder and bowel dysfunction, sexual disturbances, fatigue and depression.

Other practical approaches of current problems in neurology will be taken care of in workshops devoted to neuropathic pains and to new developments in treatment of headache.

Practical breakfast sessions on clinical neurophysiology have been included this year with hands-on sessions on EMG, nerve conduction studies and transcranial Doppler.

The scientific programme will start on

Monday morning with the first poster session, with scientific papers selected from abstracts submitted for presentation. Two different approaches to problems posed by management of stroke will be considered, the one in a teaching course, the other during the Presidential Symposium.

During the integrated teaching courses on diagnosis and treatment of dementia, management of stroke and disorders of the peripheral nervous system, selected scientific papers related to the topics will be presented.

Symposia on the molecular era of muscle disorders; pathophysiology of epilepsy, advances in diagnosis and treatment of Parkinson's disease and critical issues in multiple sclerosis will also take place during the meeting. Last but not least, oral and poster presentations with walking tours and interviews with presenters of scientific papers on various topics selected from the abstracts submitted will illustrate the vitality of neurology in Europe. ♦

Visit the ENS 2009 website

www.akm.ch/ens2009

- Continuously updated scientific programme
- Online registration as well a hotel & tour registration
- Option to compose your personal congress programme
- Details about the industrial exhibition and symposia arranged with the industry
- Information about Milan

Preparation for the 2009 ENS meeting, which will be held in Milan, June 20-24, is nearly complete. Only the programme of free scientific communications is still to be settled. The meeting will start on Saturday, June 20 with workshops on neurosonology, treatment with Botulinum toxin, early diagnosis of motor neuron disease, mild cognitive impairment and hyperkinetic movement disorders. The second part of the morning programme includes workshops on demyelinating disorders in children, neurological complications of HIV infection, disorders of gait and rehabilitation. Half-day teaching courses will start on Saturday afternoon with courses on neurology in internal medicine; differential diagnosis of multiple sclerosis; neuroimaging; intensive care in neurology; and management of the dizzy patient.

Courses and workshops at the 2008 meeting in Nice were very rewarding, with rooms completely filled with neurologists in training. Young neurologists are encouraged to apply for ENS support to attend the meeting, especially the teaching programme. Thanks to our

Nineteenth Meeting of the
European Neurological Society








June 20–24, 2009

Milan, Italy

Neurology: Learning, knowledge, progress and the future

Key symposia:

-  Management of stroke: from bench to guidelines
-  The molecular era of neuromuscular disorders
-  From pathophysiology to new treatments in epilepsy
-  Parkinson's disease: advances in diagnosis and treatment
-  Critical issues on MS diagnosis and treatment

The congress programme includes interactive case presentations, 23 teaching courses, 16 workshops organised by the ENS subcommittees, practical breakfast sessions in clinical neurophysiology and selected scientific sessions in the form of oral sessions, poster sessions (guided poster walks) and satellite symposia.

Abstract Submission Deadline: February 11, 2009

Early Registration Deadline: April 22, 2009

For further information please contact:

ENS 2009, c/o AKM Congress Service

Association House, P.O. Box, CH-4002 Basel / Switzerland

Phone +41 61 686 77 77 Fax +41 61 686 77 88 Email info@akm.ch

www.ensinfo.org

EDITOR'S CHOICE

MOTORNEURON DISEASE: helpful neighbours

Amyotrophic Lateral Sclerosis (ALS) is a form of motorneuron disease characterised by the loss of lower and upper motorneurons. It is a fatal condition for which effective therapies are desperately needed. In this study in *Nature Neuroscience*, it has been shown that non-neuronal cells can help- namely astrocytes when transplanted into the cervical spinal cord of SOD mutant rats caused increased motor neuronal survival with accompanying functional benefits in the grafted animal.

In this study, a particular type of astrocyte was used- GRPs, which represent a lineage-restricted precursor cell derived from the developing spinal cord. These cells were then labelled with GFP and transplanted into the cervical cord of 90 day old SOD rats. This site for grafting was chosen because one of the major causes of death in ALS is respiratory failure secondary to diaphragmatic weakness.

After grafting, about a third of the cells survived and differentiated into astrocytes with little evidence that they proliferated post implantation. There was some time-dependent migration of the cells away from the graft site but the benefits were largely restricted to the

forelimb and diaphragm- both of which improved with the cell grafts.

So how do astrocyte transplants help protect neurons from death? Well the answer relates to the fact that the grafted cells express a glutamate transporter (GLT1, which is equivalent to EAAT2 in humans) which is normal and functionally active, unlike the host astrocytes. In addition these cells can reduce microgliosis but do not produce growth factors for the motorneuron.

This study is therefore of interest as it shows that cell therapies for neurodegenerative disorders of the CNS may need to use cells other than those directly targeted by the disease process. So given the recent interest in glial mediated cell death, what disease is next going to be treated by astrocyte, rather than neuronal, grafts?

– RAB

Lepore AC, Rauck B, Dejea C, Pardo AC, Rao MS, Rothstein JD, Maragakis NJ.

Focal transplantation-based astrocyte replacement is neuroprotective in a model of motor neuron disease.

**NATURE NEUROSCIENCE
2008;11:1294-301.**

REHABILITATION: Memories are made like this

We all take photographs and even sometimes make home videos so that we will have reminders of events or moments in our lives. The pictures also provide a way of sharing past experiences and can sometimes trigger memories we haven't thought about in ages.

These aide memoirs are often used to try to bring back memories in those who have amnesia due to head injury or conditions such as Alzheimers disease. Now a group in Cambridge has shown how using photographic film shows of significant days in an amnesic patient's life can help to consolidate autobiographical memory.

Their case, 'Mrs B', a 63 year old well educated woman with bilateral hippocampus lesions following limbic encephalitis, has marked amnesia. She usually has no memory of events after a couple of days. The Cambridge group developed a camera, called SenseCam, which is worn on the chest and takes images every 30 seconds. The resulting film, shot from the point of view of the first person can be replayed, discussed and shared.

The effectiveness of using the SenseCam films was compared with keeping a diary record of special days. After six viewings 80% of events were recalled from the Sensecam days and 49% were recalled from the diary

days. While it might not be surprising that the films were better for recall it was remarkable how effective they were over the long term. Retention of events was maintained three months later and without viewing SenseCam images in the mean time. Events from days recorded using the diary were not remembered at all even at one month.

The camera training was welcomed by Mrs B and her husband. Importantly it enabled them to share experiences and it also helped her to be less anxious about forgetting important times.

This is a very simple and effective strategy for aiding memory but it proved to be more than that. It also demonstrates how important context is in consolidating memories. I look forward to seeing how this works with other amnesic patients. – AJT

Berry E, Kapur N, Williams L, Hodges S, Watson P, Smyth G, Srinivasan J, Smith R, Wilson B, Wood K.

The use of a wearable camera, SenseCam, as a pictorial diary to improve autobiographical memory in a patient with limbic encephalitis:

**A preliminary report
NEUROPSYCHOLOGICAL REHABILITATION
2007;17:4,582-601.**

Journal reviewers

Heather Angus-Leppan,
Royal Free & Barnet
Hospitals;

Chrystalina Antoniadis,
Cambridge Centre for Brain
Repair;

Roger Barker,
Cambridge Centre for Brain
Repair;

Lloyd Bradley,
Colman Centre for Specialist
Neurological Rehabilitation
Services in Norwich;

Alasdair Coles,
Cambridge University;

Andrew Lerner,
Walton Centre, Liverpool;

Mark Manford,
Addenbrooke's Hospital,
Cambridge and Bedford
Hospitals;

Wendy Phillips,
Addenbrooke's Hospital,
Cambridge;

Robert Redfern,
Morrison Hospital, Swansea;

Ailie Turton,
University of Bristol.

Call for Reviewers

Would you like to join ACNR's panel of journal reviewers? All we need is a short summary and personal comment on any interesting articles you read in your specialist journals. Share your thoughts with ACNR's 5000 readers in the neurological community. For more information E. Editorial@acnr.co.uk

COGNITION: muscling in on memories

Long Term Potentiation (LTP) in the hippocampus was described for the first time over 30 years ago and since then much has been written about it in terms of its molecular/synaptic basis. The phenomenon describes the increase in synaptic transmission at the CA1 synapse in response to an intense afferent input. Whilst the exact mechanism causing it is not fully understood, key players have been identified and include the post-synaptic NMDA and AMPA receptors, with activation of the former leading to an increase in the latter via a calcium-dependent process. A recent paper by Wang et al suggests a mechanism. They show that the influx of calcium through the NMDA receptor activated myosin Vb, which in turn recruit recycling endosomes in the dendritic spine that move to the cell membrane where they cause spine growth and the insertion of more AMPA receptors. This transportation of receptors and membrane is done via actin filaments, which is a calcium dependent process.

This work uses a number of different approaches to confirm that this network is causally linked to LTP at this synapse, and as such provides a fascinating new insight into LTP. In particular it highlights the extent to which neurons can restructure small parts of their dendritic tree and by so doing mediate focal synaptic changes reflecting if you like a degree of "microplasticity". This brings with it a level of complexity to the dynamic remodelling of the CNS that could not have been conceived of when LTP was first coming to scientific attention. – **RAB**

Wang Z, Edwards JG, Riley N, Provance DW Jr, Karcher R, Li XD, Davison IG, Ikebe M, Mercer JA, Kauer JA, Ehlers MD. Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity.

CELL

2008;135:535-48.

STROKE: My brother had a bleed in his brain....

It is a standard conversation in clinic: what are my risks of having a subarachnoid haemorrhage (SAH), given that my [XXX relative(s)] had one? It is pretty clear that the risk of having an unruptured aneurysm, or a subarachnoid haemorrhage, is marginally increased if a first-degree relative has had a SAH. But what about the risk of a SAH if two or more first-degree relatives have had one? Up until now, there has been no clear answer, because you need a huge study to identify sufficient numbers of people with lots of affected relatives.... Step up the nation of Sweden. By using the Swedish Inpatient Register and the Swedish Multi-generational Register, 130,373 relatives of people with SAH were identified. The headline result is that your chance of having a SAH with one relative affected is increased by 2.15 and for those with two affected first-degree relatives, the odds ratio was 51.0. The absolute risk is still pretty low.... around 10 per 100 000 person-years. And the odds-ratio of 51 is not as hard as might first appear; it is based on only 1 affected in the controls and 10 affected in the "multi-relatives" group. We should not moan: it is unlikely we will ever have a bigger study to address this question. The clear result is that we should take people seriously when they ask for aneurysm screening, if more than one first-degree relative has had a SAH. And then we get into the thorny issues of how frequently to screen, with what modality, and quite what to do with unruptured aneurysms... Not easy. – **AJC Bor AS, Rinkel GJ, Adami J, Koffijberg H, Ekblom A, Buskens E, Blomqvist P, Granath F.**

Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study.

BRAIN

2008 Oct;131(Pt 10):2662-5. Epub 2008 Sep 26.

HEADACHE: The new kid on the block for migraine

Triptans have been the mainstay of acute migraine treatment since the 1990s. Since sumatriptan, there have been innumerable other agonists of the serotonin 5-HT_{1B/1D} receptors, with some seriously improbable names ("eletriptan" is my favourite). They are genuinely useful drugs, albeit expensive. Eletriptan costs over £3 a tablet, whereas three aspirin (which my wife finds just as effective) costs 5p. The triptans also cause alarming chest pain, which is probably not due to cardiac ischaemia, and there are worries about using them in cardiovascular disease, uncontrolled hypertension, and focal migraine subtypes such as hemiplegic and "basilar migraine". Now, something genuinely new: an antagonist of the calcitonin gene-related peptide receptor. It turns out that CSF CGRP concentration is increased during a migraine attack and intravenous CGRP triggers migraine-like headaches in people with migraine.... So now, does blockade of CGRP help people with migraine? Merck funded this phase 3 RCT of 1380 patients given telcagepant, zolmitriptan, or placebo. Telcagepant was as effective as zolmitriptan at reducing migraine frequency and severity, and had fewer adverse events (37% for telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo). Quite where telcagepant acts is a bit mysterious. Lars Edvinsson, in the commentary suggests whether it works on the CGRP-containing sensory nerves of the intracranial vessels, or the trigeminal nerve, or yet more centrally... This all sounds terrific. I hate to be a party-pooper, but I would like to see a trial of telcagepant versus a NSAID. – **AJC**

Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Lebensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK.

Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial.

LANCET

2009;372(9656):2115-23

Brain Awareness Week 16-22 March, 2009

Every March the European Dana Alliance for the Brain (EDAB) coordinates Brain Awareness Week, a major collaboration celebrating the wonders of the brain and brain research through hundreds of public events worldwide.



Dr Fabio Carmello

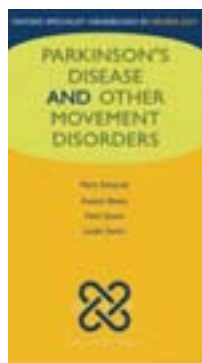
EDAB is an organisation that is committed to enhancing the public's understanding of why brain research is so important.

THE EUROPEAN
DANA ALLIANCE
FOR THE BRAIN



To find out more, visit our website
www.edab.net or contact EDAB by
phone on +44 20 7019 4914, or by
email enquiries@edab.net

Parkinson's Disease and Other Movement Disorders



Authors: M Edwards, N Quinn, K Bhatia
Published by: Oxford University Press 2008-06-03
Price: £39.95
ISBN: 978-0-19-856984-8

Reviewed by:
 Tom Foltynie, National Hospital, Queen Square, London, UK.

Dr Edwards et al are to be congratulated in having completely achieved what they set out to do, namely create a comprehensive yet portable and robust reference on Parkinson's disease and other movement disorders. This book is accessible to novices and yet contains sufficient detail about the rarities to be a valuable reminder to even the most seasoned movement disorder practitioner. The accompanying excellent DVD shows examples of all the common and many of the rarer movement disorders and will form the basis for many a teaching session for both students and post-graduates interested in the subject.

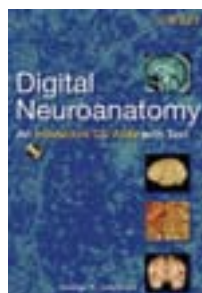
Naturally there is a large section of Parkinson's disease and atypical parkinsonisms with up to date information regarding genetic risk factors for the disease, a guide to the management of the early and later stages of the illness including the newer treatments for the condition such as the dopamine agonist patch and the intra-jejunal formulation of levodopa. There is also the necessary emphasis on the non-motor symptoms of PD including the increasingly recognised dopa dysregulation syndrome, and the role of non-medical therapies for PD.

Many of the chapters begin with "an approach to the patient with e.g. myoclonus" which describes the useful features from the history and examination to guide the

examiner towards a particular path of investigation. There are tables and lists throughout the book e.g. on the subject of tremor, the authors give appropriate emphasis to the features that distinguish tremor subtypes like essential tremor and dystonic tremor together with excellent advice regarding treatment strategies. Personally I found that the most useful features of this book are the lists of causes e.g. "Causes of dystonia with peripheral neuropathy", and descriptions of the "neurological diseases associated with acanthocytosis" and other esoterica frequently discussed but rarely seen. For those infrequent moments when I need to check how to introduce medications for Wilson's disease, I also now know where to look! The final chapter covers psychogenic movement disorders, often the most challenging group of patients to diagnose and manage, and gives very useful advice regarding techniques to help confirm the diagnosis at the bedside and most importantly the strategies for management in terms of communication, withdrawal of medications and introduction of non-medical therapies.

This book fits nicely in my briefcase, weighs next to nothing and is both quicker and a more useful way of accessing movement disorders related information than even Google. I thoroughly recommend it. ♦

Digital Neuroanatomy



Author: George R Leichnetz
Published by: Wiley-Liss Publishing
Price: £46.95
ISBN: 978-0-470-04000-3

Reviewed by:
 John Bowen, Consultant Neurologist, Lincoln County Hospital, UK.

If, like me, you were rubbish at art at school you probably reacted to your Art Report with a similar combination of sniffy dismissiveness, pseudo-scientific disdain for the impossibility of defining 'art' itself let alone what constitutes quality in the stuff, and a grudging acceptance of the comment that whilst effort had been acknowledged by teacher, the fruits have admittedly been, well .. underwhelming. An especially bad year would invoke various accompanying barbed epithets you know the sort of stuff, "shows little interest and less talent", "against fierce competition quite the worst pupil I can recall", "may do better to try the hairy end of the brush", that sort of thing. Well I now appreciate poor Mr Bennett's task. Not the Pride & Prejudice one, but my old art teacher.

This book has the stated aim "to present what is considered that every medical student should know about neuroanatomy taught in wet laboratory in a first year neuroscience course.... [but] does not purport to be an exhaustive presentation of this subject material...our medical students have a second-year course in which pathology of the brain is discussed more extensively." Hmmm.

So what you get here is 77 pages moving through light microscopic neurohistology, e-m neurohistology, skull, meninges & cord, brain (gross), brain (sectional), and introduction to MRI (including a few tumours – an interesting conceptual leap bypassing the small matter of clinical neurology and fertilizing the rampant growth of disbelief that "all you need is one of them "MIR" scans, Doc" as my dustbin man regularly advises me when I put the wrong coloured bin out each week.

Well frankly the pictures in the book are poor. The black & white photos add to the sense of histology lab

gloominess that helped to uninspire most of my undergraduate chums (who could face neurohistology and actually turned up!)

I still have my undergraduate LM/ and gross neuroanatomy text (Structure of the Human Brain 2nd ed, S.DeArmond et al: New York OUP 1976) and it is far superior. Though admittedly lacking either EM or MR chapters this ring bound folder far exceeds anything this book has to offer. Similarly, if you are going to teach / learn neuroanatomy with MR technology, and I see no reason not to, the pictures need to be better than this. Radiological anatomy books of far greater quality already exist.

Which leaves the CD-ROM and let's be honest we all like a CD-ROM. Well this is quite fun admittedly and clearly set out and easy to navigate. The macroscopic images are of good quality, in colour, and well labelled. Again the MR images are pretty ordinary and irritatingly the macroscopic correlative slices overlap the radiographic images. One can click a bit & see the answer which is how it should be but it could be so much better. For example click the bit and see in glorious colour the interconnections both anatomical and functional (colour coded by neurotransmitter red for GABA, green for Dopamine, I could go on...) enlarging phoenix-like from the 2-D image rather than click A - hippocampus click B - fornix etc etc.

I suppose the hook of a CD may attract a few well off medical students to buy this out of curiosity but I would probably not have been one of them. Had one of my chums acquired a copy I would have "borrowed" the CD though, as it is a more enjoyable (and therefore more effective) way to learn. In summary, fair effort could do better B-. ♦

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.com

Laser TIRF 3 Imaging System

With the introduction of the Laser TIRF 3 microscope system, Carl Zeiss enhances the capability of scientists to visualise near-cell membrane dynamic processes while maintaining optimum specimen incubation conditions and single molecule dynamic processes in cell-free systems. In combination with other techniques, such as Atomic Force Microscopy (AFM), it provides a complete solution for users in the life sciences, biochemistry, molecular biology and biophysics arenas.

The Laser TIRF 3 maintains Carl Zeiss' long-standing commitment to system flexibility. A range of incubation options maintain viable conditions for live cell experiments. Together with the Definite Focus module, users can be assured of accurate quantitative data over long time periods. The new laser module may be equipped with up to four solid-state lasers, is AOTF-controlled (Acousto-Optical Tuneable Filter) and may be operated entirely from the AxioVision software interface.

The TIRF slider is available in two versions; either manual or fully-motorised and software controllable. The motorised version permits a given illumination angle to be set with significantly greater accuracy and speed than other current systems and the reproducible angle setting results in reproducible penetration depths for the light beam. Together with the corrected beam-path and special filter sets, the apochromatically-corrected optics of the TIRF slider guarantee maximum image quality.

AOTF control and angle setting are integrated into the 'Fast Image Acquisition' module of the AxioVision software, enabling significantly more high resolution images to be acquired within any given timeframe.

For more information E. micro@zeiss.co.uk



S-Nerve™ ultrasound tool a real boon for paediatric anaesthesia

Sheffield Children's Hospital was the first facility in the UK to acquire a SonoSite S-Nerve™ tool, SonoSite's point-of-care ultrasound tool designed specifically for anaesthesia. Dr Nigel Pereira, consultant paediatric anaesthetist, is now routinely using the streamlined system for needle guidance in a range of nerve blocks.

"We use our S-Nerves in theatre, where we perform almost the full range of paediatric specialty surgeries. I think it is an excellent instrument, and the whole team has been very pleased with it. The S-Nerve offers the specific features we want with the same impressive resolution as SonoSite's other ultrasound systems."

"We have a MicroMaxx® system in the ICU, where the portability is a real benefit. In theatre it is more practical to keep the S-Nerve tools mounted on their stands. I am a relative novice in ultrasound, but I find the S-Nerve very intuitive



and straightforward, and the large screen and minimal controls are an advantage. Always having it available is a great boon."

For more information
T. 01462 444 800, E. europa@sonosite.com
W. www.sonosite.com

Residents at Glenside complete sponsored walk for charity

Despite undergoing continuing rehabilitation for various brain injuries and neurological conditions, 10 residents at Glenside Manor tested themselves as they walked varying distances to raise money for charities of their choice on 30th September last year. Some managed a few hundred metres and others completed 3 laps of the Glenside site in South Newton, Wiltshire – raising in the region of £600 in the process for 4 charities; Headway, Barnardo's, Anna's Room and Pets as Therapy. Ray Barnes, who is determined not to use his wheelchair for short distances, was the catalyst for the event and was successful in getting 9 others to join the walk. Previously a successful Civil Engineer, Ray sustained a brain injury during a woodland mountain bike ride 2001. He has undergone rehabilitation in Southampton, Winchester and now Glenside where he has progressed so much that he lives in one of the 10 bungalows, specifically designed to provide 'supported independent living' where nursing and care staff are on hand round the clock. The walkers are all undergo-



ing their own rehabilitation programmes (with Physiotherapy, Psychology, Occupational Therapy and Speech and Language Therapy, all provided by the therapy teams on-site).

For more information
E. Jlindley@glensidemanor.co.uk

Azilect® slows the clinical progression of Parkinson's disease

Preliminary results of the ADAGIO trial were presented at the European Federation of Neurological Societies (EFNS) 12th Congress, Madrid, Spain, on 26th August 2008. The ADAGIO trial showed that Azilect® (rasagiline) slows the clinical progression of patients with Parkinson's disease. In the trial, newly-diagnosed patients with Parkinson's disease (PD) showed sustained clinical benefits at 18 months compared to patients in whom treatment had been delayed by 9 months.

These results could have a significant impact

for patients newly diagnosed with Parkinson's disease as the trial suggests that early treatment with Azilect® has a significant and sustained clinical benefit in the longer-term.

"We are excited by the preliminary results of the ADAGIO trial. The data show that early treatment in PD can result in a slowing of clinical progression. These data are also consistent with an earlier trial with rasagiline which showed a similar outcome. This may offer real benefit to patients who are treated promptly after diagnosis," said Professor

David Burn, Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle University and UK ADAGIO study investigator.

Azilect® has been available on prescription to patients in the UK since July 2005. Previous studies have shown that Azilect® benefits the symptoms of PD in both the early and later stages of PD and that it is well tolerated.

For further information contact Teva on
T. 01296 719 768.

If you would your news to feature in ACNR, please contact Rachael Hansford, T. 01747 860168, E. rachael@acnr.co.uk

First Twin-Scanner Multiphoton Microscope

Zeiss has overcome the challenges of imaging deep inside living tissues with the launch of the LSM 7 MP, a purpose-built multiphoton laser scanning microscope that, for the first time, incorporates two separate scanners. The twin scanners mean that the system's two excitation lasers can be set to different wavelengths and used either simultaneously or sequentially for specimen imaging and manipulation.

Because the LSM 7 MP uses longer-wavelength, femtosecond lasers and the scan modules are optimised for excitation light up to 1100 nm, efficient fluorescence excitation deep inside tissue samples is possible without the phototoxic damage associated with high intensity light. The LSM 7 MP can be used with up to five, sensitive non-descanned detectors in reflection or transmission mode or both. Simultaneous use of two detectors in the transmission and reflection modes delivers a high-



er signal yield than with a single detector and allows the excitation laser intensity to be minimised. Used with either the non-descanned detectors or the special GaAsP non-descanned detector taken directly from the recently-introduced LSM 710 NLO, the LSM 7 MP is ideal for the observation of structural changes in whole, live animals.

Other application fields include high resolution 3D imaging in long-term observations of development processes and functional imaging in conjunction with simultaneous photo-manipulation. A wide range of detectors, filters and other accessories allow every user to configure a personalised and application-specific system and the entire system is quick to set-up and easy to use thanks to the intuitive ZEN imaging and control software.

For further information
E. micro@zeiss.co.uk

Neuromodulation News winter issue



The latest issue of Neuromodulation News is now available. Neuromodulation News is pleased to feature in this issue articles by Dr Walter Paulus on tDCS and interviews with Dr Marco Davare and Niamh Kennedy, the winners of Magstim's Young Investigators Awards 2008. Dr Heidi Johansen-Berg reports on the Magstim TMS Summer School 2008, and the date for the Magstim TMS Summer School 2009 is confirmed as the 29th – 30th May 2009. In addition, there is a round-up of news stories covering aspects of neuromodulation and brain stimulation, as well as an events diary for those working in the fields of Neuroscience and Neurology.

Neuromodulation News provides an overview of new or interesting developments in the fields of neuromodulation and brain stimulation, with articles written by scientists and researchers involved in these sectors. If you would like to suggest an article or content for the next issue of Neuromodulation News please contact the editor.

For your free subscription to Neuromodulation News, please send your full postal address and preferred e-mail address to editor@neuromodulationnews.org, with "Neuromodulation News Subscription" in the subject line.

Neuromodulation News is sponsored by The Magstim Company Ltd.

The Ring Chromosome 20 Foundation

After years of testing, misdiagnosis, and a difficult journey to find medical treatment, the Ford family was told that the reason their young daughter Cara was having frequent and severe seizures was because of ring chromosome 20 epilepsy syndrome. With so much uncertainty and little information about the syndrome available, Cara's father, Stewart Ford, decided to establish a Foundation to fund medical research and other projects so that families and doctors can better understand this condition and its treatment.

The purpose of the Ring Chromosome 20 Foundation is to promote awareness of the syn-



drome and the importance of chromosomal testing in children with refractory epilepsy. The Foundation is based in London and in New York City and is currently funding genetic and clinical research. Initial results were presented at the American Epilepsy Society (AES) meeting in Seattle 5-9 December, 2008.

However, there is still an urgent need for more patients to be identified through medical professionals around the world.

To register a patient and take part in current research, or find out more information about this syndrome please visit www.ring20.org.

Nikon expands advanced imaging solutions to include SEM

Nikon Instruments Europe and JEOL have announced an agreement that appoints Nikon as the official European distributor of the innovative NeoScope benchtop SEM (scanning electron microscope).

Whether used by trained electron microscopists as a compact screening instrument, or by lab technicians seeking a higher resolution alternative to the light microscope, the NeoScope will help accelerate the pace of research in all fields. Offering simplicity and affordability along with benchtop convenience, the NeoScope is ideal for use in the areas of sampling inspection, failure analysis of manufacturing materials, materials research, metallurgical laboratories, medical devices, forensics, bioscience research, pathology and environmental laboratories



Welcoming the new agreement, Bill Clement, Industrial Sales Manager at Nikon Instruments commented, "The NeoScope is a fresh new approach offering a powerful yet affordable benchtop SEM. By offering the NeoScope togeth-

er with Nikon's microscopes and digital cameras, we are able to offer a comprehensive range of imaging and inspection solutions from nano- to micro- to macro-features."

An entirely new advanced imaging tool, the NeoScope makes it straight forward to obtain images of high magnification, high resolution and large depth of field using a microscope that is as simple to operate as a digital camera, with the powerful electron optics of an SEM. A wide range of samples and materials can be loaded and imaged quickly and conveniently.

For more information please contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu W. www.nikoninstruments.eu/neoscope

COPAXONE® (glatiramer acetate)
PRE-FILLED SYRINGE PRESCRIBING
INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered subcutaneously once daily. **Children (12 – 18 years)** No specific studies. Data suggests safety profile similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy, Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipoatrophy). An immediate post-injection reaction (one or more of vasodilatation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, hyperhidrosis, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £545.59. **Product Licence Number** – 10921/0023 **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB **Date of Preparation** – September 2008.

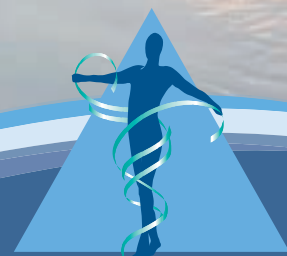
Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.

Adverse events should also be reported to

Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Reference: Ford C. et al. *Multiple Sclerosis* 2006; 12: 309-320.
Date of preparation: December 2008 Code: C0807/428f

Your decision today can make a difference tomorrow



COPAXONE®
(glatiramer acetate)

TEVA


sanofi aventis
Because health matters

Long-term active