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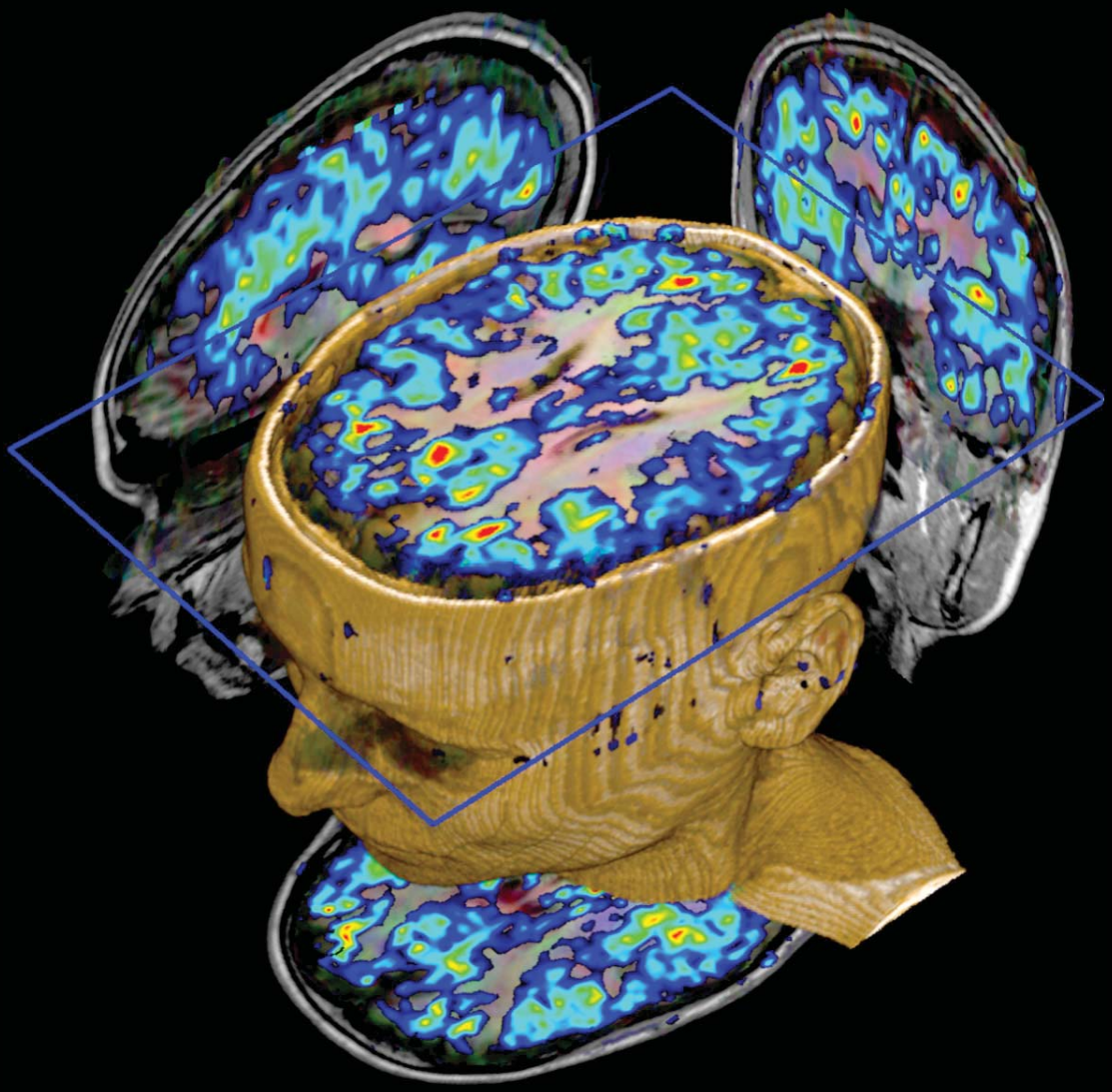
Advances in Clinical Neuroscience & Rehabilitation



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Conference and Society News • Journal Reviews • Diary of Events

TIME TO SWITCH THEIR OFFS TO ON'S

PARKINSON'S

APO-go: treatment for PREDICTABLE symptoms of Parkinson's disease

Use APO-go Pen early in treatment plan for rapid reversal of impending "off's". Simple, easy to use sc injection

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"Intermittent apomorphine injections may be used to reduce off time in people with PD with severe motor complications."

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ABRIDGED 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 diseases 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** Not recommended for use in women of child-bearing potential or in nursing mothers. **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 and 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 while driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa when given concomitantly with 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 transient. 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. Transient mild confusion and visual hallucinations have occurred during apomorphine therapy, and neuropsychiatric disturbances may be exacerbated by apomorphine. The use of apomorphine HCl in conjunction with levodopa treatment may cause Coombs' positive haemolytic anaemia. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. 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: 05928/0020 APO-go Pens: 05928/0021 APO-go Pre-filled Syringes: 05928/0025 **Legal Category:** POM. Date of **Last Revision:** February 2006. For further information please contact: Britannia Pharmaceuticals Limited 41-51 Brighton Road, Redhill, Surrey RH1 6YS APG.API.V5

BRITANNIA Pharmaceuticals Limited

www.apomorphine.co.uk

Information about adverse event reporting can be found at www.yellowcard.gov.uk Adverse events should also be reported to Medical Information at Britannia at the above address or telephone: 01737 773741 or e-mail drugsafety@forumgroup.co.uk

APG.AD.BLPen.V1 Date drawn up: April 2007

In the last issue of the ACNR we had a critique of the recent ABN guidelines on disease modifying therapy in MS by Neil Scolding and colleagues as part of our controversies in Neurology and Neuroscience series. In the next issue we hope to publish the ABN response to this, but in the meantime my co-editor Alasdair Coles debates this issue further in his journal review of the BENEFIT study.

Professor Simon Baron Cohen, in his short review on autism, highlights the key issues in this not uncommon disorder - up to 1% of the population lie somewhere on the autistic spectrum. The cause of this condition is not known but various models and genetic influences are discussed in this article, along with some suggestions on how best to manage individuals with it. This short review article written by such an acknowledged expert is extremely informative and helpful.

It is very common to be asked to see a patient who has collapsed in order to establish the cause and instigate appropriate treatment. Often, however, the case remains a conundrum and undiagnosed. In their excellent review article Joe Anderson and Phil Smith take us through their approach. They conclude that "misdiagnoses are common and that the best way to avoid this is to retake the history from different sources and at different times, and to resist premature diagnoses".

Dr Ravishankar, in an illuminating review article on headache in India, reveals why there are problems in the diagnosis and treatment of this common disorder in a country with 16% of the world's population. As he comments, "headache medicine is still not a recognised sub-specialty in India and myths and misunderstandings abound. Headache patients end up being seen by many different specialists, each one of whom looks at the problems through the window of their own specialty. For all these reasons, headache patients in India do not receive adequate sympathy, care and attention." This is the first in a new series on Neurology in India edited by Dr Khadikar and promises to offer unique insights into a different world of neurological practice.

If you had a spare £1.5 million would you invest in magnetoencephalography (MEG)? Dr Rugg-Gunn explains why we may want to do this, as he discusses the merits of this technique in neurological practice – especially epilepsy. This article is the first in a new series on emerging neurophysiological techniques edited by Dr Andy Michell and this is well-illustrated in this excellent first article.

The review by Chong and Hester makes for sobering reading. They take as their theme the evidence base of medical treatment of trigeminal neuralgia which is shaky at best. However, this comprehensive review makes it clear that there are treatments worth trying in this condition, and this includes interesting new data on the use of triptans. This article nicely complements the one we had recently by Professor Coakham on the surgical treatment of this disorder.

In the series on the patient perspective, Steve Pape discusses the mental problems of a serious head injury. Steve survived a horrific motor bike accident and whilst making great progress with his physical disability struggled with a mixture of cognitive and affective difficulties. His account therefore delineates with great clarity these problems, highlighting how he readjusted to them after a major head injury and how complicated and unrecognised these are in contrast to the physical disability that such patients experience. This theme is to some extent taken up by the two articles of Andrew Hanrahan and Christine Collin and Lloyd Bradley.

In their article, Andrew Hanrahan and Christine Collin highlight the value of long term rehabilitation therapy by taking us through the case history of a young man with Wilson's disease who over the course of four years of therapy went from being "totally dependent" to obtaining a degree and being able to "run, swim and play some sport".

Lloyd Bradley, on the other hand, explores the issue of the "soul" in Doctor Faustus by Thomas Mann. This fascinating essay discusses the issues of what defines people, their soul, and how this can be understood through literature and the neurological disorders of fictional characters and what this may mean in patients with brain injury.

The diagnosis of a vasculitis of the CNS is a difficult one to make and included in this is the problem of defining the extent and basis of that vasculitic illness. Mark Walker discusses all this in his contribution to our Neuropathology series, highlighting the salient features of the different types of vasculitides and illustrated with a plethora of instructive pathological images.

Andrew Larner continues his series on neurological signs, this time taking as his subject carphologia or floccillation. If you are not sure what these terms refer to then read this article, so that you do not mistake them for self harm!

Our sponsored article on Drugs in Neurology explores the value of glatiramer acetate as a disease modifying therapy in patients with relapsing remitting multiple sclerosis especially in patients who have failed beta interferon treatment for whatever reason.

We hope you enjoy this new issue of ACNR - do feedback to us on our articles, especially the controversies and finally, don't forget to look at the list of latecomers to the neurologists ball.

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

Latecomers to the Neurologists' Ball

Thanks to everyone for their suggestions for Latecomers to the Neurologists' Ball.

Mr and Mrs dular-nystagmus and their daughter penny dular-nystagmus - *Peter Sandercock*

Signor & Mrs Zumab and their high maintenance daughter Natalie - *Giles Elrington*

Mr and Mrs Aplexy and their very serious daughter Cat. The word on the street is that she's going out with the sleepy Irishman, Mark O'Lepsy. Mr and Mrs Ign-intercranial-hypertension and their son Ben. Oh look, he's come with the oldest member of the Piloedema family - yes, that's Pa Piloedema. In the Parkinson's party I can see Brad Ykinesia greeting his continental guests: from Spain, El Dopa, and from France, the Comte D'inhibitor. And last, but not least, Mr and Mrs Ter-headache and their eye-watering son Klaus. - *Mark Weatherall*

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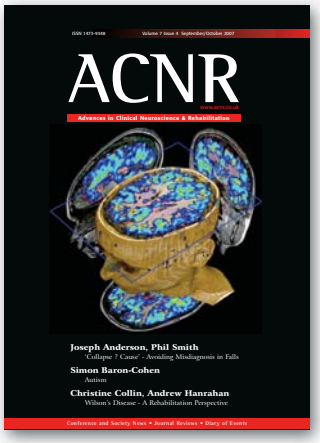

Cover picture:
Siemens is the first company to develop a complete commercial ASL (Arterial Spin Labelling) solution with the University of Pennsylvania. ASL is an application which enables perfusion imaging without the use of contrast agents. With this patent, Siemens will introduce syngo ASL, powered by Tim (Total imaging matrix), thereby allowing a broad range of users in both the clinical and research settings to get access to this promising application. In the image, syngo ASL acquired with 64 x 64 matrix and 5 mm slice thickness, fused in the Neuro 3D card with structural MR data.

Additional web content www.acnr.co.uk

Case Reports:

Epilepsy and related conditions
Complex Partial Seizures Masquerading as Depression
Dr Pooja Dassan, July 2007.

Miscellaneous
Pregabalin in the Treatment of Visual Hallucinations in Charles Bonnet Syndrome
Dr Kathryn Bundle, Mayur Bodani, Dr Lal Landham, June 2007

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September/October 2007

NEW EXTENDED LICENCE

As monotherapy or in combination with levodopa...

Neupro®

rotigotine transdermal patch

The Parkinson's Patch

...Neupro delivers.

Neupro® Rotigotine.
Prescribing information.
Presentation: Neupro® is a thin, matrix-type square transdermal patch.
Neupro 2 mg/24 h transdermal patch:
Releases 2 mg rotigotine over 24 hours.
10 cm^2 patch contains 4.5 mg rotigotine.
Neupro 4 mg/24 h transdermal patch:
Releases 4 mg rotigotine over 24 hours.
20 cm^2 patch contains 9.0 mg rotigotine.
Neupro 6 mg/24 h transdermal patch:
Releases 6 mg rotigotine over 24 hours.
30 cm^2 patch contains 13.5 mg rotigotine.
Neupro 8 mg/24 h transdermal patch:
Releases 8 mg rotigotine over 24 hours.
40 cm^2 patch contains 18.0 mg rotigotine.
Indications: To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy. **Dosage:** Neupro is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. In monotherapy, treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week (e.g. 2 mg/24h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. In combination with levodopa, treatment initiation is at 4 mg/24 h and increased weekly in 2 mg increments, up to a maximum dose of 16 mg. **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Warnings and Precautions:** External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. **Undesirable effects:** Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry mouth, dyspepsia, hyperhydrosis, erythema, pruritus, asthenic conditions and peripheral oedema. Uncommonly, syncope, loss of consciousness, visual disturbances, or hypotension may occur. Rarely, psychotic disorders, increased libido or convulsion may occur.
Basic NHS Cost: Starter Pack: £110.34
2 mg Continuation Pack of 28 patches: £77.24
4 mg Continuation Pack of 28 patches: £88.28
6 mg Continuation Pack of 28 patches: £110.34
8 mg Continuation Pack of 28 patches: £142.79
Legal Category: POM. **Product Licence Number:** EU/1/05/331/001-013. **Product Licence Holder:** SCHWARZ PHARMA Ltd, Shannon Industrial Estate, Shannon, Co. Clare, Ireland. **Date of preparation:** December 2006. (NEU3898). Neupro® is a registered trademark. Prescribers should consult the Summary of Product Characteristics for the full information on side-effects, warnings and precautions. Further information is available from SCHWARZ PHARMA Limited, 5 Hercules Way, Leavesden Park, Watford, WD25 7GS, United Kingdom. **Date of literature preparation:** January 2007.

Information about adverse event reporting can be found at www.yellowcard.gov.uk
Adverse events should be reported to the Drug Safety department at
SCHWARZ PHARMA Limited (UK) on 01923 684 100 or drugsafety@schwarzpharma.co.uk

SCHWARZ PHARMA

NEU3887a

'Collapse ? Cause' - Avoiding Misdiagnosis in Falls

Introduction

'Collapse ? cause', 'fall', 'syncope', 'blackout', 'drop attack' and '? fit' are terms all commonly used by healthcare staff and patients to describe events leading to emergency presentations. Clinicians and patients often lack accurate understanding of these terms and their implications; they may be used synonymously or mean different things to different people. 'Collapse' implies either transient loss of consciousness (TLOC) or a fall without loss of consciousness.

- TLOC is usually caused by syncope, seizure or a psychogenic event. Syncope is an abrupt and transient loss of consciousness resulting from sudden impairment of cerebral perfusion, but the term is frequently misused to include falls without loss of consciousness. 'Faint' and 'blackout' are looser terms, often used interchangeably for syncope.
- Falls without loss of consciousness are subdivided into collapses and 'mechanical falls', e.g. from impaired mobility or during a sporting activity. Both are commonly mislabelled as 'syncope' despite retained consciousness.

The cause of collapse must be accurately identified for both clinical and socio-economic reasons. In practice, such judgements often rest with the most junior medical and nursing staff. Misdiagnosis is common, usually through incomplete history taking and examination, or failure to recognise vital clues, e.g. ECG abnormalities, or through making premature diagnoses (mostly of epilepsy).

Scale of the problem

In 2005/6, there were 82,999 admissions in England with 'syncope and collapse' (302,969 bed days), with mean patient age of 67 years [1]; these figures will only rise further with an ageing population. Fractures provide an even more striking example of the socioeconomic cost of falls: in Wales alone 4,200 hip fractures occur annually, costing £84 million, with 7% of such patients dying in the first month and 25% within one year.[2] Clearly, secondary prevention is essential for patients who have fallen. Probably the most costly misdiagnosis is the incorrect labelling of patients with epilepsy,[3] estimated at costing the NHS £138 million per annum,[4] not to mention the far-reaching consequences for individual patients.

Clinical Assessment

Emergency

Any patient who has fallen requires detailed assessment but the priority, as with any emergency presentation, is airway, breathing and circulation (ABC). Any patient who is short of breath, has chest pain, acute headache or significantly abnormal vital signs, clearly needs urgent assessment and treatment. Pulmonary embolism, myocardial infarction and subarachnoid haemorrhage (amongst others) are diagnoses not to miss.

History

If the patient is stable, the most important step is to obtain a reliable history of the event and of any prior falls. This may not be possible if the patient is confused, drowsy or amnesic, e.g. from a head injury, and witness accounts should be sought. Unfortunately, in busy emergency settings the most crucial components are often overlooked, leading to misdiagnosis. Particularly important is the

Box 1: Important history pointers in the falls patient

- *Did the patient lose consciousness or not?*
- *If so, for how long? Was the recovery immediate, fast, or delayed?*
- *Were there precipitating environmental or physiological triggers (e.g. prolonged standing, hot environment, micturition, fear)?*
- *Were there warning symptoms (e.g. aura or pre-syncope)?*
- *Is there any witness description?*
- *Did anything suggest a mechanical aetiology (tripping, trauma, weakness)?*
- *Was there inter-current illness (e.g. sepsis, diabetic ketoacidosis, hypoglycaemia, Addison's disease, haemorrhage)?*
- *Were there neurological disturbances affecting balance, gait, or movement (e.g. vertigo, ataxia, parkinsonism, visual impairment)?*

Dr Joseph Anderson, MB, ChB, is a Neurology SHO at the University Hospital of Wales, Cardiff, with an interest in epilepsy, syncope and collapse. He aims to complete Core Medical Training and move into higher training in Neurology in the near future.

Dr Phil Smith, MD, FRCP is a consultant neurologist in the University Hospital of Wales, Cardiff with a principal clinical interest in epilepsy. He is the Trust's Associate Medical Director for Training and Education, Regional Neurology Programme Director, and Honorary Secretary of the Association of British Neurologists.

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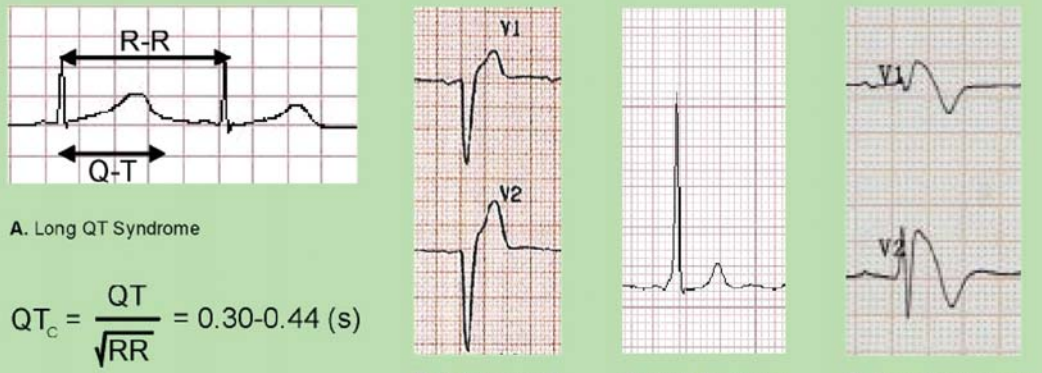
Fax. 029 2074 4166

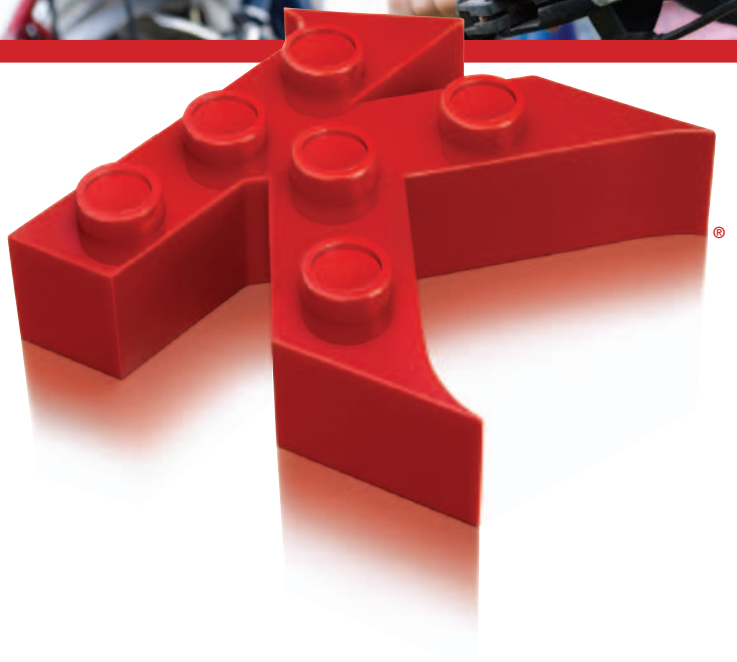
Resources

- www.stars.org.uk has a Blackouts Checklist endorsed by DoH for free download.

Figure 1. ECG abnormalities assosciated with syncope and sudden death.



(A) The corrected QT interval is calculated as shown.
(B) Pathological Q waves in leads V1 and V2 indicating prior myocardial infarction predisposing to scar related VT.
(C) Wolff-Parkinson-White Syndrome (Type A) characterised by a short PR interval and the classic slow rising delta wave.
(D) The classical ECG complex seen in Brugada syndrome shows a 'pseudo right bundle branch block' pattern and a unique ST elevation pattern seen in leads V1-V3.



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KEPPRA® 100 mg/ml concentrate for solution for infusion
Active Ingredient: *Tablets:* levetiracetam 250, 500, 750 and 1,000 mg. *Oral Solution:* levetiracetam 100 mg per ml. *Infusion:* levetiracetam 100 mg per ml. **Uses:** Monotherapy for partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy for partial onset seizures with or without secondary generalisation in adults and children from 4 years of age, for myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy and for primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. *Infusion:* an alternative for patients when oral administration is temporarily not feasible. **Dosage and Administration:** *Oral solution:* should be diluted prior to use. *Infusion:* Keppra concentrate must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15 minute infusion. *Monotherapy (adults and adolescents from 16 years):* Recommended starting dose of 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily. *Adjunctive therapy: Adults and adolescents older than 12 years or weighing 50 kg or more:* 500 mg twice daily can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg:* 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations see SPC.) *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended, as the creatinine clearance may underestimate the renal insufficiency. **Contraindications, Warnings etc.:** *Contraindications:* Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. *Precautions:* If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the *oral solution* may cause allergic reactions (possibly delayed). *Infusion:* Keppra concentrate contains 7.196 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. *Interactions:* Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. *Pregnancy and lactation:* Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. *Driving, etc:* Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (≥10%): asthenia/fatigue, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability/mood swings, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets:* None. *Oral solution:* Store in original container. After first opening use within 2 months. *Infusion:* Use immediately after dilution. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. Solution x 300 ml: EU/1/146/027, Infusion (500 mg/5 ml) x 10 vials: EU/1/00/146/030. **NHS Cost:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. Solution x 300 ml: £71.00, Infusion (500 mg/ 5ml) x 10 vials: £135.00. **Name and Address of PL Holder:** UCB S.A., Allée 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: medicalinformationuk@ucb-group.com
Date of Revision: January 2007
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Date of preparation: July 2007.
07KP0056d

ucb CNS INNOVATORS™

search for evidence of structural heart disease or arrhythmia. This is especially true where the history includes syncope during exercise or whilst lying down, syncope with palpitations, a family history of sudden death or a history of heart disease (especially previous myocardial infarction). These patients require prompt cardiology assessment. Clinicians should resist the temptation to make a premature diagnosis, when repeated history taking, the passage of time, and future witness accounts might clarify the situation. The most salient history points are summarised in Box 1.

Having documented the fall, the clinician should seek associated factors; careful inspection of the patient's medication is crucial to this. Neuroleptics, antidepressants, sedatives, diuretics and antihypertensive medication consistently increase the risk of falls, mainly through sedation, imbalance and postural hypotension. Certain medications may prolong the QT interval,[5] so promoting cardiac syncope. Those (especially older) persons taking four or more medications are at greatest risk of falling; reducing their number of medications reduces their fall frequency.[6] Information about the patient's home and surroundings, in particular stairs, carpets, etc. is also important; these may contribute to falls in those with impaired mobility and represent modifiable risk factors that, if missed, can exacerbate misdiagnosis.

Examination

The patient who has fallen requires a thorough examination, particularly for evidence of injury, and cardiovascular or neurological abnormalities.

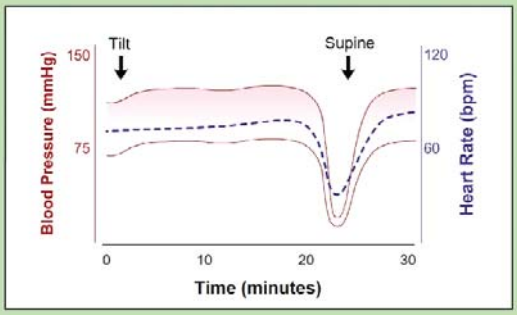
- Evidence of injury will include head trauma and fractures, particularly in the elderly.
- Cardiovascular examination. A crucial part of the falls assessment is to measure the lying and standing blood pressure (BP). This is primarily to detect orthostatic hypotension, particularly in elderly patients. Orthostatic hypotension is a fall in systolic BP of at least 20mmHg within three minutes of standing.[7] This usually reflects autonomic failure due to systemic disease such as diabetes mellitus or alcohol toxicity, but may occur (with orthostatic pre-syncope) as an isolated finding in the elderly. Commonly it is caused or worsened by inter-current illness (dehydration, Addison's disease, etc.) or drugs (see above). Although often performed and recorded, it is rarely done adequately. Most patients first undergo BP measurement lying down and then a single measurement immediately after standing, usually without heart rate measurement. This may identify some patients with orthostatic hypotension and may usefully correlate with the patient's presenting symptoms but a negative result would not exclude orthostatic hypotension. The patient should remain standing for at least three minutes, with repeated BP measurements if there is no drop, in order to increase its sensitivity. The heart rate should also be measured, as this fails to change in autonomic failure despite the BP fall (Figure 2).
- Neurological examination can reveal much about the cause of falls yet this part of the assessment is often done poorly. Patients (especially the elderly) are rarely asked to walk in emergency settings despite the recommendation to perform the 'get up and go' test.[6] Asking the patient to rise from a chair without using the arms, walk a few steps and then return, identifies those who need further assessment and intervention. This is especially true since dyspraxia may not be revealed by bedside examination. A full neurological examination should reveal gait abnormalities, visual loss, extra-pyramidal signs, ataxia and weakness that might contribute to falls. In reality however, the examination will be normal in most falls patients, especially those with syncope.

Investigations

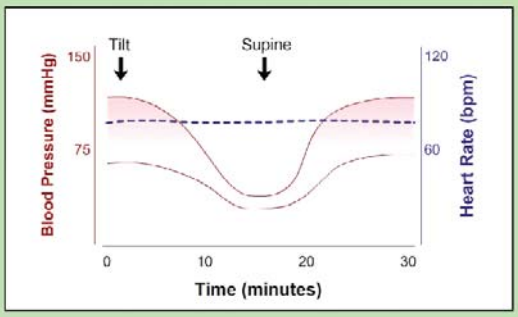
Electrocardiogram (ECG). An ECG is mandatory for all patients with unexplained falls. Clinicians dealing with patients who have fallen should recognise and actively seek certain specific ECG abnormalities.[8] These may be rhythm or conduction abnormalities but the most important are those signalling susceptibility to sudden cardiac death, namely long QT syndrome, pathological Q-waves (indicating susceptibility to scar-related ventricular tachycardia), Wolff-Parkinson-White syndrome and Brugada syndrome (Figure 1).

Head-up tilt-table testing is a useful investigation in recurrent unexplained syncope, having the advantage of a controlled environment, providing accurate physiological data, and allowing correlation of the patient's symptoms with their physiological signs. Its primary role is to identify those patients with a propensity to vasovagal syncope and those with suspected delayed orthostatic hypotension. Orthostatic hypotension symptoms and signs may be delayed for 10 or more minutes,[9] posing a diagnostic challenge and contributing to misdiagnosis. Where the suspicion of orthostatic hypotension remains high despite negative bedside testing, or there are repeated high-risk falls, the patient should be considered for head-up tilt-table testing. Examples of the typical responses in vasovagal syncope, orthostatic syncope and postural orthostatic tachycardia syndrome are shown in Figure 2.[10]

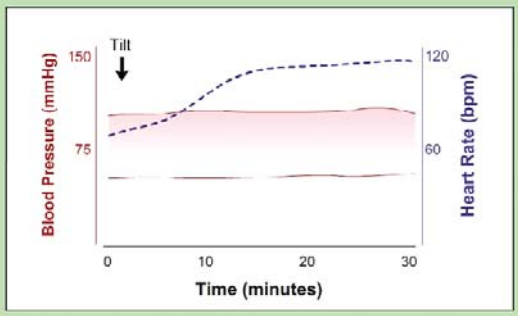
Figure 2. Examples of abnormal physiological responses in Head-Up Tilt-Table Testing



A. Vasovagal Syncope - There is an ubrupt fall in heart rate and blood pressure occuring after a significant period of 60 degree upright tilt.



B. Orthostatic Hypotension - The blood pressure slowly begins to fall soon after tilting but there is failure of the normal compensatory increase in heart rate.



C. Postural Orthostatic Tachycardia Syndrome (POTS) - Defined as an orthostatic intolerance associated with an increase in heart rate of more than 30bpm or to greater than 120bpm within 10 minutes of standing.

Common pitfalls

Transient ischaemic attack (TIA). A major misconception is that loss of consciousness might represent a TIA; in fact it virtually excludes it. This misdiagnosis is commonplace in elderly patients or those with vascular risk factors and leads to unnecessary investigations such as carotid Doppler studies and even angiography. As the clinician has already identified these patients as high risk, the investigation often finds significant and treatable disease, but its management does not help the patient's falls. As in epilepsy clinics, specialist TIA clinics receive many referrals of patients who have suffered syncopal episodes.

Epilepsy. Many patients with falls from vasovagal or cardiogenic syncope are misdiagnosed as epilepsy: the literature suggests around 20%.[11] This creates serious problems: patients may be prescribed potentially danger-

ous long-term medication, be subject to driving and lifestyle restrictions and even social stigma, and all the while their actual diagnosis remains untreated. The error is particularly likely when syncope is convulsive. Brief myoclonic jerks or reflex anoxic seizures are poorly recognised as normal consequences of impaired cerebral perfusion. This might then be compounded by over-interpretation of minor electroencephalogram (EEG) abnormalities.

Psychogenic non-epileptic seizures (pseudoseizures) are commonly misdiagnosed as epileptic seizures, and less commonly vice versa. As many as 50% of patients with apparent status epilepticus have pseudoseizures or 'pseudostatus'[12] and are often intubated and managed on intensive care units. This may arise from an over emphasis on features such as incontinence, tongue biting, and unresponsiveness being suggestive of epileptic seizures, or may reflect under-recognition by medical staff of the prevalence of pseudoseizures, which are not well covered in undergraduate teaching. Indeed, this may be felt to be the case for functional disease in general.

Avoiding misdiagnosis

Misdiagnosis of patients who have fallen is common and often has significant consequences. Much of this can be avoided by a systematic approach to the history and examination and by awareness and understanding of the differential diagnosis of falls and the pathophysiology involved, e.g. in convulsive syncope. The crucial but often overlooked aspects of assessment include a detailed medication review, examining the patient's gait and looking carefully for orthostatic hypotension when the clinical suspicion is high. Early involvement of allied healthcare professions such as physiotherapy and occupational therapy, as well dedicated 'falls' teams in some hospitals, aim to identify individual factors contributing to falls and to limit future risk. The best way to avoid misdiagnosis is to retake the history, from different sources and at different times, and to resist premature diagnoses. This is especially useful in suspected epilepsy where increasingly patients are directed to specialist services in an attempt to limit misdiagnosis. Useful care pathways have been suggested to provide a framework for managing these patients in different environments.[3]

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Autism

Autism is a spectrum condition, in that it manifests in varying degrees of severity. At one extreme, a person may have no social skills, no language, and major learning difficulties. At the other end of this spectrum, a person may have normal or even above average IQ, precocious vocabulary development (though a lack of interest in small-talk or chatting), and social skills that are only odd by virtue of being one-sided or extremely self-centred. The former case would receive a diagnosis of classic autism. The latter case would receive a diagnosis of Asperger Syndrome (AS). Both represent subgroups on the autistic spectrum. Both also share a strong preference for routines and repetition, and where the intellectual style narrow and deep – an 'obsessional' interest in highly specific topics. Up to 1% of the population are somewhere on the autistic spectrum.

Psychological aspects

The empathising-systemising (E-S) theory[1] proposes that there are empathising deficits in autism, whilst systemising is either intact or superior. Empathy involves imagining another person's thoughts and feelings and having an emotional reaction that is appropriate to that other person's feelings. Children and adults with AS show their empathising deficits on age-appropriate tests.[2] This deficit underlies the difficulties in social and communicative development and in imagining others' minds. Systemising is the drive to analyse a system in terms of underlying rules, in order to understand and predict its behaviour. People with autism spectrum conditions show precocious understanding of systems, relative to their mental age.[3] The unusually strong repetitive behaviour, the strong desire for routines, and the 'need for sameness', can be seen as the result of the person's strong drive to systemise. Systemising also requires excellent attention to detail, and people with autism and AS are faster on visual search tasks.[4] The strong systemising underlies the strengths that people with autism and AS have.

Neurobiological aspects

Anatomical abnormalities have been identified in many brain areas in autism. These include the cerebellum, corpus callosum, hippocampus, and the amygdala. Epilepsy also occurs in classic autism. In terms of neuropathology, the number of Purkinje cells in the cerebellar cortex is abnormally low.[5] Abnormalities in the density of packing of neurons in the hippocampus, amygdala, and other parts of the limbic system have also been reported.[6]

Functional neuroimaging suggests increased activity in sensory areas of the brain normally associated with stimulus-driven processing, and decreased activity in areas normally associated with higher-cognitive processing.[7] Abnormalities in autism have also been found using functional neuroimaging in the amygdala, the orbito and medial frontal cortex.[8] These atypical pattens of neural activity are associated with the empathising deficits. Using either MRI volumetric analysis, or measures of head circumference, the autistic brain appears to involve transient postnatal macroencephaly.[9]

Genetic and hormonal aspects

The sibling risk-rate for autism is approximately 4.5%, or a four-fold increase over general population rates. Regarding twin studies, when a narrow phenotype is considered, 60% of MZ pairs are concordant for autism vs. no DZ pairs. When a broader phenotype is considered, 92% of MZ pairs are concordant vs. 10% of DZ pairs.[10] Molecular linkage genetic studies have led to several chromosomal regions being identified, such as 2q, 7q, and 15q (22-24). Loci on the X chromosome have also been implicated in autism, which may explain the sex ratio in autism (markedly biased towards males).[11] The marked sex ratio in autism may also reflect hormonal factors. Currently there are clues that foetal testosterone (FT) may play a role: within normal development, FT is inversely correlated with frequency of eye contact, rate of vocabulary development, empathy and social skills, and FT is positively correlated with narrow interests and systemising.[12]

Early diagnosis and intervention

The earliest age at which classic autism has been reliably diagnosed is at 18 months of age, following a screening using an instrument called the CHAT (Checklist for Autism in Toddlers) which tests for the absence of 'joint attention' behaviours such as pointing and gaze following, and the absence of pretend play, all behaviours that are normally present by this age.[13] Asperger Syndrome has been reliably diagnosed by age five years, following a screening using an instrument called the CAST (Childhood Asperger Screening Test).[14] The most effective interventions for children with autism or AS are special education, such as social skills teaching, and Applied Behavioural Analysis (ABA), where appropriate skills and behaviours are taught through principles of reinforcement.[15] The key ingredients for effective early intervention are that the methods are highly structured, intensive, and individualised. Appropriate cognitive interventions are also beneficial for teenagers and adults. Medical treatments are not usual, and there are ethical issues surrounding the notion of trying to 'cure' autism, since whilst some aspects of the condition do require help (e.g. the empathy difficulties), other aspects may not (e.g. the systemising talents).

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Resources

- The National Autistic Society is the main charity in the UK for families with a child on the autistic spectrum: www.nas.org
- The Autism Research Centre, Cambridge University, contains a searchable database of publications and screening instruments such as the CAST, AQ, and CHAT: www.autismresearchcentre.com
- As interventions are scientifically evaluated, the results of such studies are summarised at www.researchautism.net

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Wilson's Disease - A Rehabilitation Perspective

Introduction

Wilson's disease (WD) is a rare autosomal recessive inborn error of metabolism due to a defective WD gene, ATP7B, located on Chromosome 13q,[1] which causes low levels of the copper binding protein, caeruloplasmin. Spontaneous mutations are common. Copper accumulates in the liver, cornea and basal ganglia due to loss of the binding protein, reduced hepatic transport and reduced biliary secretion of copper.

Untreated Wilson's disease (hepatolenticular degeneration) is a relentlessly progressive and ultimately fatal disorder. A timely diagnosis and co-operation with lifelong specific treatment removes the copper, prevents re-accumulation and prevents or treats the liver and brain damage.

Wilson's disease is not usually presented from a rehabilitation perspective. This account describes the clinical journey of a 23-year-old man with WD, who deteriorated catastrophically after initial penicillamine therapy. He needed intensive long-term neurorehabilitation for severe neurological and cognitive impairment that for some time looked irreversible. Although there are excellent reviews of the initial medical treatment of Wilson's,[2,3] there is little available on rehabilitation outcomes[4-7] and even less on evidence-based practice.

Case history

Presentation and treatment

This man presented with a six-month history of mild dysarthria, an asymmetric 'tapping' tremor at rest in his right hand, incoordination on walking and running, minor personality changes and uncharacteristic underperformance in his preceding year at University.

He moved stiffly, spoke softly and had variable rigidity of the right upper limb with dystonic hyperextension of the right thumb and tremor. Kayser-Fleischer (KF) corneal rings were seen and confirmed on slit lamp examination. His serum caeruloplasmin was very low at 4mg/dl (normal >20); serum copper was low, 5mmol/L. (normal 11-24) and 24hr urinary copper excretion (with precautions to avoid contamination) was high with an average of 16.6mmol/24hr (normal<0.9). MRI brain scans showed typical abnormalities. His full blood count, renal parameters, and liver function tests were normal.

His parents were unrelated and there was no relevant family history. A diagnosis of Wilson's disease was confirmed. UK experts were consulted and involved in due course. Genetic testing found he was a compound heterozygote for two mutations of the Wilson gene, 524_525delAA and H1069Q and his siblings were then also screened. He was prescribed penicillamine, and started a low copper diet.

Deterioration

Within a week he developed a widespread erythematous rash, a moderate fever and loss of appetite, a sensitivity reaction which occurs in approximately 20% of individuals and usually resolves. His neurological condition then deteriorated quickly and dramatically. This is a known complication.[8] He was bed-bound, his penicillamine was discontinued and he was readmitted as an emergency.

His voice was low volume and dysarthric with perseveration. Information processing, attentional skills, concentration and memory were all impaired contributing to reduced executive function. Eye movements and tracking were slowed and jerky. He had severe cervical dystonia, his swallowing was impaired and he needed nasogastric feeding. He had marked rigidity in all four limbs with extreme dystonic flexion in his neck, right hand and right foot, severe resting tremor in his right thumb and hand, and mild left sided tremor. He was unconcerned with transient urinary and faecal incontinence. He was 'moody', uncooperative with therapy interventions and suspicious of hospitals and doctors.

Further management

Trientine, an alternative chelating agent was started, and benzhexol was continued. UK experts were consulted repeatedly over his management. He was severely disabled, was referred urgently for neurorehabilitation, and began intensive treatment 19 days after the onset of his reaction to the penicillamine.

Neurorehabilitation

He had inpatient neuro-rehabilitation for over twelve months with goal setting, regular case conferences and involvement of his family. Initially there was no significant change in his severe disability. Reference to a few case reports on the potential for late neurological and cognitive recovery encouraged the team and family that an intensive rehabilitation programme was worth pursuing.[9-11]

Verbal output was whispered, dysarthric and perseverative. He had severe antecollis with drooling and unsafe swallowing. Botulinum toxin injections into neck muscles improved head positioning from a marked tilt to the right to a lesser tilt to the left. The complexities of dealing with this dystonic, akinetic rigid state with cognitive impairment were becoming apparent.

Strategies to deal with mood swings, disinhibition and mildly sexualised behaviour were introduced by the psychologist and were partially successful. He remained distractible with poor concentration and attention skills for many months. Insight was slow to improve, as was his speed of information processing which came up from <1st percentile two months after diagnosis to the 16th percentile some eight months later.

Zinc acetate was introduced, after careful consideration and wide consultation, some seven months after his diagnosis was made, to try and speed up an intractably slow rate of change in his condition. This appeared to be associated with a faster rate of recovery. Zinc induces enterocyte metallothionein, promoting enteral binding of copper and slowly increases faecal copper excretion.[12] Careful dosing schedules avoiding interaction between trientine and zinc are necessary for maximal effect. He tolerated this combination well, although compliance was to become a significant issue.

His dominant right thumb was painfully dislocated at the MCP joint and was severely dystonic. After much discussion it was wired and splinted after a trial of Botulinum toxin. Botulinum toxin injections were also used repeatedly to reduce dystonia in the short and long flexors of his right foot, neck muscles, and forearm and hand muscles, with overall success. Throughout, he had serial splinting to his contractures, intensive physiotherapy and bespoke orthoses. The early goals were to maintain, or regain, muscle length and passive range of movement at all joints. A powered wheelchair helped his mobility and mood, and reduced his social isolation.

His initial Barthel ADL (Activities of Daily Living) Index score was 1/20 (totally dependent) and had only improved to 6/20 after three months of intensive reha-

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bilitation (continent, could shave with set –up, could feed using his left hand, and was no longer being hoisted for transfers) At six months his Barthel Index had improved to 11/20. He was using a power wheelchair, assisting with dressing, and transferring using a Rotunda turning frame. Distractibility and low mood were still preventing full cooperation. He began to practise walking first with a pulpit frame, then with two physiotherapists supporting and guiding him in the gym and in hydrotherapy. Progress remained slow due to dystonic contractures worse on the right side.

Improving range of movement was hindered by pain. The use of entonox (equal parts of nitrous oxide and oxygen) allowed examination and treatment under analgesia, demonstrating that movement was possible in an apparently dystonic, rigid and severely contracted limb. Although mutual trust had been re-established, changes in medication were still viewed with suspicion.

At twelve months he was walking independently with a wide based gait, upper body stiffness, head turned to the left, with contractures of right arm and leg, and postural tremor in the right leg. His toes were clawed. Botulinum injections to the long and short flexors of the right foot allowed him to get his foot flat on the floor for the first time. Left sided movements were now well coordinated with good hand function. The right hand was not functional. His Barthel had improved to 18/20. He needed help dressing his dystonic right foot, and could not cut up food. He had much greater insight into his cognitive impairments, was beginning to use strategies for poor memory, and could discuss his illness sensibly. He was encouraged to monitor his own progress, plan his own day and follow an exercise programme.

When his University were made aware of his illness they reconsidered his University record and decided to award him his degree. He became our first inpatient to obtain a degree while in hospital. Despite his progress it was clear that, at the end of inpatient rehabilitation, he had many unmet needs as well as potential for further improvement. He was not convinced and initially rejected our efforts to secure long term funding for further residential rehabilitation to work on vocational needs and independent living.

Outcomes

At the end of a year, he was discharged home to live with family. Compliance with medication, while sometimes erratic, was reasonable. Local outpatient therapy services were inadequate. This distressed him, his family and his inpatient team. Paradoxically, it helped secure funding and his cooperation to move on to a vocational placement.

After one year in a specialist residential rehabilitation centre he was keen to stay on for a second, reflecting significant improvement in cognitive skills and insight. He left in April 2007 and now lives independently using practised strategies to manage his time, monitor his mood and deal with periods of frustration and aggression.

Physically, he can run, swim and play some sport. He has been left with an abnormal posture of his dominant right hand. This is monitored; repeated treatments with Botulinum toxin and stabilising hand surgery have given him a functional improvement in grip and flexion control.

Cognitively there has been substantial recovery of his general IQ, memory skills, sustained and divided attention. He is still slow at processing new information. He is able to monitor speed and volume of speech, and communicates competently most of the time. Impulsive behaviour, distractibility and anger still occur but he manages them more effectively. He is now looking at supported employment options through 'Ways into Work'.

Discussion points

1. Recovery is slow and protracted

Wilson's disease is rare, affecting 1:30,000 of the population worldwide.[1] Few neurorehabilitation teams have experience in its management. At the start of this man's rehabilitation journey his future looked bleak. An unwritten goal was to secure his full cooperation, that of his family and the treating team. The evidence as there was, suggested that a good outcome could be achieved. Four years after becoming symptomatic he is still improving.

2. Do no harm

Another unwritten goal was to do no harm – good clinical practice. The ease with which one dystonic deformity could be converted into another with Botulinum toxin, introduced a high degree of caution into our practice. Early hand surgery to correct deformities without addressing function, e.g. cosmetic tenotomies, could have been destructive. Frequent inter-specialty discussions maximised his prospects for a better recovery of muscular control.

3. Early treatment is not simple – consult the experts

Initial treatment of Wilson's disease presenting with neuro-psychiatric symptoms is controversial.[13-15] Penicillamine has been the mainstay of treatment but there is a risk of early neurological worsening, possibly due to rapid mobilisation of copper from the liver and its redistribution to the brain. It may be transient but can be catastrophic. In penicillamine intolerance or as first line treatment, trientine alone or a combination of trientine and zinc is now used. Once the central nervous system has been 'de-coppered', either trientine or zinc is continued long term. Lifetime surveillance and success of treatment is judged by serial 24hr urinary copper, serum copper levels and, in most instances, by the disappearance of KF rings. At all stages the management of this young man followed best advice and available evidence. Dimercaprol treatment was suggested shortly before his discharge from neurorehabilitation. Being able to cross the blood-brain barrier, it could remove copper directly from the brain and perhaps stimulate further cognitive recovery. He considered the side effects of dimercaprol carefully and decided against it, with family support.

4. The patient and family are central to the large team of experts required for optimal recovery

His family was pivotal in anchoring his recovery and was the base from which his needs were evaluated and met. The people involved in his recovery were a truly multidisciplinary team. They included neurologists, nationally respected Wilson disease experts, a multi-disciplinary neurorehabilitation team, a hand surgeon and his team and lastly, life skills and vocational experts.

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Thomas Mann's Doctor Faustus and the Flight of the Soul

The myth of Doctor Faustus has taken on many incarnations since its first appearance as a folk tale in medieval Germany. The cautionary tale of an individual who makes a pact with the devil to exchange his soul for personal fulfilment appears in different guises throughout the world, and has embedded itself in the language of today. One of the most heinous crimes an artist can be accused of is "selling your soul" i.e. the loss of some individual or esoteric element contained within an artistic form in order to satisfy mass appeal and thus reap personal reward.

The contemporary retelling of this story, *Doctor Faustus* (1947) by Thomas Mann, subverts this idea, somewhat, in that its protagonist, the composer Adrian Leverkühn, makes a pact with the devil in order to gain a mastery of contemporary musical forms. Mann's book is a complex and dark work that places the myth of Faustus within a 20th century setting. The story of Leverkühn's pact with the devil is set against a backdrop of Germany coming to terms with the First World War and its aftermath, fermenting the social and political environment that led to the rise of Nazism. Mann left Germany in 1933 and did not return until 1949. During this period he wrote *Doctor Faustus* (as well as *The Holy Sinner*), and there are clearly analogies between the ominous undercurrents present in the book and the development of certain elements of German society in the years leading up to the Second World War.

Along with its historical, religious and political dimensions, *Doctor Faustus* uses different neurological illnesses as devices to develop the story in a modernist sense. The existence of a real, physical devil, for example, cannot be utilised in the way that it could be for an earlier audience.

The syphilis, which is contracted from a prostitute in Leverkühn's early life, may be used, through the development of neurosyphillis, to explain the delusions that he experiences and which, perhaps, underlie his artistic genius. His meeting with the devil, when it comes, is described as a prolonged hallucination, with the devil adopting various different physical forms and speech patterns through the encounter, as he persuades Leverkühn that by forgoing love he will overcome his artistic stagnation. There is a suggestion that Leverkühn is aware that the "devil" he is conversing with is a creation of his own mind;

> *"..name to me yourself the place in my brain, the fever hearth, that makes me imagine you".*

Following this encounter, Leverkühn's fame and reputation grow as his work becomes more challenging. But, as he must, he begins to pay the price for this success. He develops headaches which are recognisable as having a migrainous flavour (associated with visual phenomena, worsened by bright light and noise). His behaviour becomes increasingly unstable, and his musical compositions become more rarefied and grandiose. The development of Leverkühn's illness can, certainly, be framed within the pathological manifestations of neurosyphillis, right until the devil claims what is finally his and Leverkühn pays with his soul, through an acute event at the climax of the book, described as a "paralytic stroke".

The use of neurological disease as "punishment" both to Leverkühn (through his syphilis, migraines and stroke) as well as his beloved nephew, Nepomuk, whose death from meningitis in the pre-antibiotic era is gruesomely recounted in almost sadistic detail, has been previously explored in terms of the clinical manifestations of these illnesses.[1,2] The use of physical disease of the brain as a metaphor for the loss of the soul is, perhaps, of greater interest to those of us who work with the survivors of brain injury. The book ends with a six page epilogue which describes Leverkühn's decline and death. It is fascinating to see how he is described sans soul;

> *..not to himself did he come; rather he found himself as a stranger, who was only the burnt out husk of his personality, having at bottom nothing to do with him who had been called 'Adrian Leverkühn'.*

The Leverkühn that we are left with at the close of the book is a terrifying figure. Robbed of his independence and ability to communicate, he reverts into a state of isolation and dependency and is cared for by his mother for the rest of his days;

> *..a helpless infant, who had no longer any memory of his manhood's proud flight, or at most some very dark and obscure vision buried in his depths.*

He makes a failed attempt at suicide by trying to drown himself in a pond, which suggests some insight into his condition and its consequences, but we are left in no illusions that

> *..the spirit has fled.*

The idea of a "soul" as an entity arising from the physical substance of the central nervous system and the consequent belief that this soul can be damaged or extinguished in some way is, perhaps, why dealing with neurological disease and its consequences can be so challenging. Whereas now we can describe "deficits" in terms of neuroanatomical lesions rather than symptoms per se, this is only a relatively recent development in the nature of human understanding and it is easy to see why sufferers of neurological disease in the past may have been viewed as being "possessed" or "cursed". The range of problems that may arise following damage to the brain, from almost imperceptible cognitive changes to persistent vegetative state may change an individual's whole place in the normal social and emotional fabric of the world. While physical damage to other parts of the body may have grave physiological consequences, one cannot imagine the spiritual decay of Leverkühn becoming manifest through kidney failure or respiratory disease, for example. The metaphor of loss of central neurological function as loss of the soul is immediate and effective. The enduring strength of this metaphor underlines the responsibilities we have in treating the sufferers of diseases of the nervous system and their loved ones.

Can the essence of an individual really be surrendered through physical changes to the brain? Although it is possible to quantify cognitive and functional changes through a battery of tests and ratings scales it is impossible to elucidate fully an individual's "nature". The friends and family of those able to leave hospital following severe head trauma will often report that "he's not the man he was". The terror evoked by Leverkühn's twilight state is enhanced by the mystery surrounding his condition. While we are never going to be able to point to an area on MRI or PET scans and identify it as "the soul", our ability to be explicit about the consequences of and possible recovery patterns from specific neurological events may rob Mann's central metaphor of some of its power.

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Clinical neurophysiology is one of the lesser known medical beasts, small enough to pass unnoticed, yet diverse enough to throw up surprises. EMG and EEG form its backbone, but what of the less well understood branches that are continually evolving and moving in new directions? This new series takes us on a tour of some of these exciting new avenues, ably guided by some of the experts responsible for shaping them. The aim of each article is to provide an overview of a new technique and discuss its role in clinical practice, both now and in the future. In this exciting series we are starting with a discussion of magnetoencephalography (MEG) by Fergus Rugg-Gunn. In future issues we can look forward to hearing about electrotonus, fMRI-EEG, single pulse electrical stimulation and other techniques – words which at present may carry no meaning for some readers, but all will be revealed in the fullness of time.

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Magnetoencephalography – Current Use and Future Applications

Magnetoencephalography (MEG) is a non-invasive neurophysiological technique that measures the magnetic fields generated by intracellular neuronal currents in the brain. The recorded magnetic field pattern is analysed to determine the localisation of either spontaneous, for example epileptic, or evoked, for example, somatosensory, neuronal activity. The resulting map of magnetic dipoles is typically superimposed on a co-registered MRI scan to facilitate accurate neuroanatomical localisation.

The first MEG recordings of cortical activity took place in 1968 using a single channel biomagnetometer. Data from a large number of recordings was averaged to elucidate normal resting alpha activity. In the late 1970's, a number of important advances, including the construction of specially shielded rooms to reduce interference from ambient electromagnetic noise, the development of gradiometers which measure magnetic field gradients rather than the actual field and the introduction of superconducting quantum interference devices (SQUIDs) greatly improved the sensitivity of MEG. These innovations permitted, for the first time, the detection of spontaneous and evoked neuronal activity (Figure 1).

More recently, whole head magnetometers comprising up to 275 sensors have been developed which through more extensive spatial coverage produce greater accuracy of dipole localisation and spatiotemporal propagation within an acceptable time period.

The magnetic fields detected by MEG originate from dipolar intracellular currents associated with dendritic inhibitory and excitatory post-synaptic potentials within sulcal pyramidal neurons orientated tangentially with the cortical surface. MEG is insensitive to radially orientated neurons located on the gyral crown, which comprise approximately one third of cortical neurons, and which dominate the EEG. The magnitude of the magnetic fields produced from about 10^4- 10^5 synchronous potentials, typical for an evoked auditory or somatosensory response, is in the order of 100 femtotesla, with epileptic activity in the region of 1-2 picotesla (Figure 2).

MEG has high temporal resolution, in the milliseconds range, which is comparable to EEG, and favourable to functional MRI which has a temporal resolution of several seconds. Modern multi-channel, whole-head MEG systems possess good spatial resolution; in the order of <5mm localisation error, with a mean scattering of source localisations of 10mm for neocortical generators, compared to a mean scattering of 20mm for EEG. In addition, magnetic fields are less distorted by the resistive properties of the skull and scalp and retain localisation accuracy following craniotomy and resective surgery. MEG is, however, an expensive investigative tool with a modern multichannel whole-head magnetometer, shielded room, liquid helium and computer hardware costing in the region of £1.5 million. This is beyond the reach of all but the most dedicated specialist units.

Clinical Applications

Epilepsy

The clinical potential of MEG was first demonstrated in studies of patients with epilepsy with the detection and localisation of, for example, rolandic spikes using single channel detectors. Currently, the main application of MEG in epilepsy is the characterisation of epileptic foci through the source localisation of interictal epileptiform activity,[1] although, infrequently, ictal abnormalities are recorded by chance. The sensitivity of MEG for the identification of interictal epileptiform discharges, typically spikes, is approximately 50-70%, with 89% localisation accuracy, using standard equivalent current dipole source localisation techniques (Figure 3). This is possibly further enhanced by using advanced analysis methods such as dynamic source modelling. MEG has been reported to be of superior localising accuracy to scalp EEG and of equivalent accuracy to invasive EEG recordings in predicting the epileptogenic zone in patients undergoing presurgical evaluation. In 41

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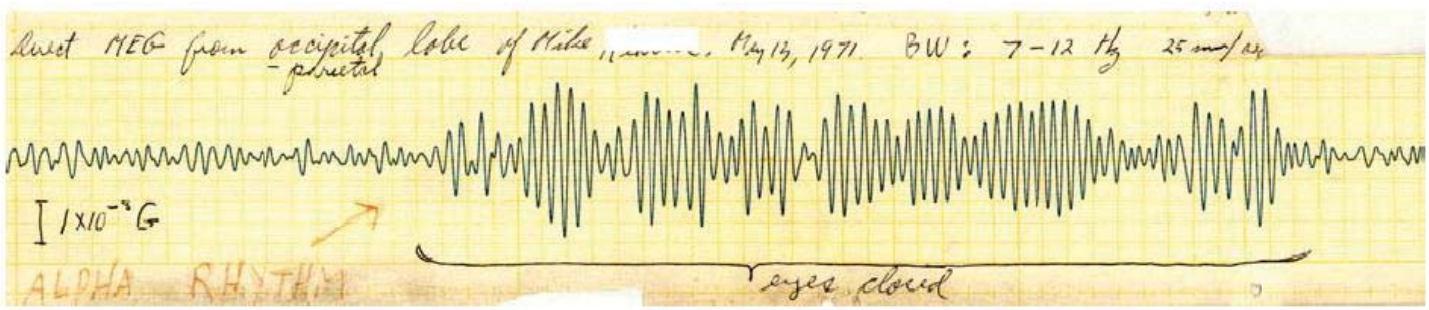


Figure 1: Single channel MEG recording of normal alpha rhythm.

patients with focal epilepsy who underwent pre-surgical evaluation the localisation accuracy, as determined by the location of surgical resection and post-operative seizure outcome, of interictal MEG was 56% compared to 54% for invasive EEG monitoring. Within this group, MEG exhibited a bias towards patients with extratemporal lobe epilepsy (65.5%).[2] This is most likely due to the improved signal to noise ratio from neocortical generators rather than deep sources. Furthermore, it has been shown that the localisation of interictal MEG dipoles correlate with ictal-onset zones as defined by intracranial EEG and complete resection of these areas predicts good post-operative seizure outcome.[3] At the present time, the information derived from MEG is complementary to data acquired from other investigations including MRI, PET and scalp and invasive EEG recordings, and, in future, may be used to guide surgical resection or more commonly, inform placement of intracranial electrodes in patients with complex refractory focal epilepsy.

Mapping of eloquent cortex

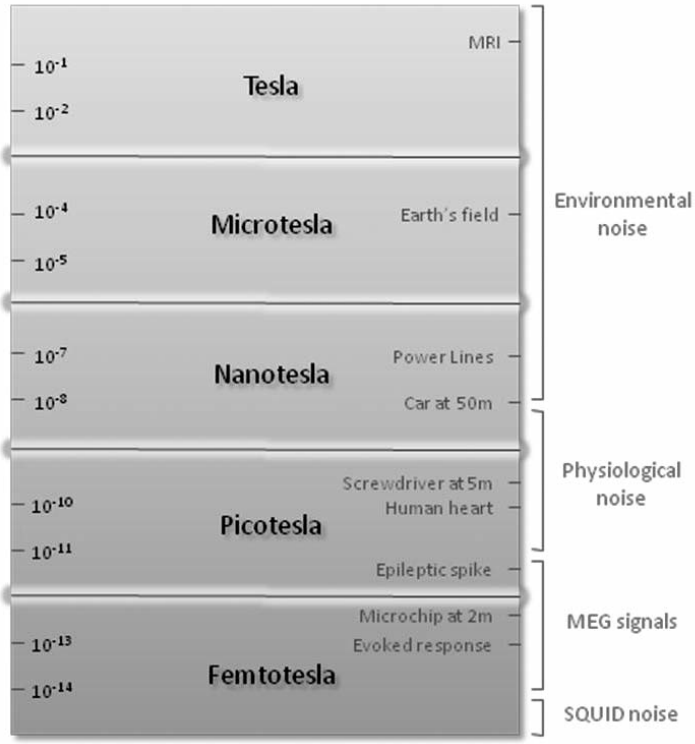
MEG has been used to map somatosensory, motor, auditory and visual specific cortex (Figure 4). The localising data from MEG may be combined with fMRI and tractography and utilised in pre-surgical planning in patients with lesions, such as tumours, adjacent to or within eloquent cortex. More recently, language mapping has been implemented and compared with intraoperative direct cortical stimulation and sodium amytal (Wada) testing.[4] MEG and sodium amytal data showed concordance in 87% of patients suggesting that MEG may be suitable for assessing hemispheric dominance for language. Functional MRI may also be used to map language function non-invasively and shows good concordance with MEG localisation.[5] In contrast to fMRI however, MEG possesses high temporal resolution and can therefore be used to characterise the propagation of cortical activation during language tasks.

MEG has also been used to investigate inter- and intra-hemispheric functional reorganisation of language areas in patients undergoing left anterior temporal lobe resection (ATLR). In a small study of 12 patients with refractory left temporal lobe epilepsy, patients with atypical (bilateral) hemispheric dominance preoperatively were more likely than patients with typical (left hemisphere) dominance to show evidence of increased right hemisphere participation in language functions after surgery. Patients with left hemispheric dominance preoperatively were more likely to show intrahemispheric changes involving a slight inferior shift of the putative location of Wernicke's area.[6] There is a paucity of MEG studies that evaluate memory function in normal subjects, and memory dysfunction in patients with conditions such as temporal lobe epilepsy or Alzheimer's disease.[7] The spatiotemporal characterisation of memory function is an important goal in, for example, the presurgical evaluation of patients with refractory epilepsy as a major concern is the potential negative effect of ATLR on memory function.

Cognitive impairment

Abnormalities of both spontaneous activity and evoked responses have been identified in patients with cognitive impairment using MEG. These studies have focused on determining the relationship between cognitive impairment and MEG abnormalities and have shown, for example, deficits in preconscious auditory processing, decreased coherence in all frequency bands and an increase in the low frequency magnetic power over the frontal and central areas.[8] More recently, in patients

Figure 2: Spectrum of magnetic field strength



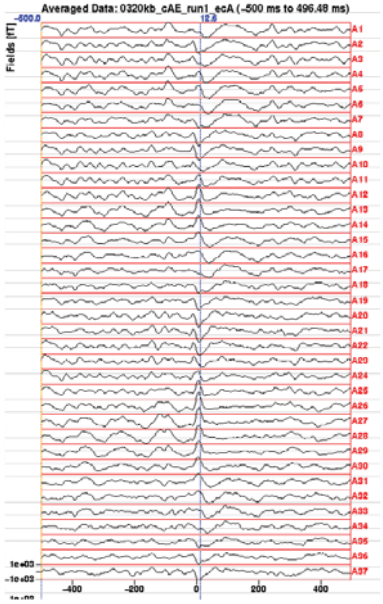
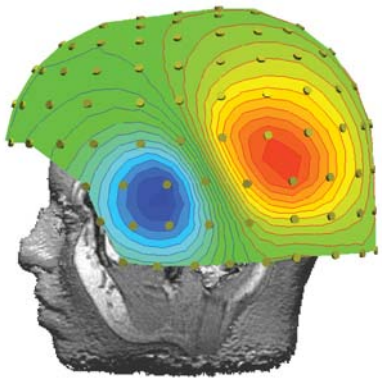
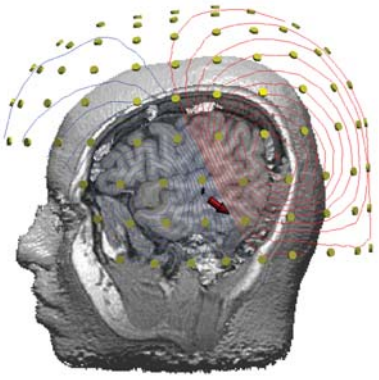


Figure 3: (Above left) Typical MEG suite showing dewar containing liquid helium and 275 recording sensors. (Above right) Recording from the first 37 MEG channels showing interictal epileptiform discharge (blue line) in a patient with focal epilepsy. (Below) Source localisation is then performed and overlaid on MR images for anatomical characterisation (red arrow).





with Alzheimer's disease, a significant correlation between the relative volume of the left hippocampus and degree of left temporal slow wave activity was seen.[9] Furthermore, left temporoparietal slow-wave activity covaried with a functional status scale whereas right temporal slow-wave activity varied with cognitive performance.[10] The degree of activation within the left temporal lobe during a simple memory paradigm correlated with left hippocampal volume in patients with Alzheimer's disease, but not in healthy control subjects or elderly patients with chronic depression and normal cognition suggesting that MEG may be of diagnostic value.[7] It has recently been shown that slow-wave activity may be present in some patients with subjective cognitive impairment only,[11] although this is not universally accepted. The functional significance of slow-wave activity in this patient group is presently unclear and future MEG studies are needed to determine whether focal slow wave activity is a specific early functional marker of AD and mild cognitive impairment or a consequence of general neuropathology.

Stroke

MEG is particularly suited to studies of stroke due to the high spatial and temporal resolution, whole-head coverage and insensitivity of cerebral generators to surrounding abnormal tissue and inconsistent neurovascular coupling that may affect investigations reliant on a haemodynamic response, such as fMRI. The earliest studies to evaluate MEG in stroke focused on the effects of cortical ischaemic lesions on the spatiotemporal propagation of somatosensory responses,[12] in particular the sequential activation of primary and secondary cortical regions. More recent studies have evaluated the possibility of "plastic" reorganisation of eloquent cortical regions following stroke. Typically, following a stroke, the MEG evoked response to, for example, somatosensory stimulation of the hand, is delayed, more widely dispersed and there is evidence of involvement of brain areas outside normal boundaries in the affected hemisphere.[13] MEG recordings of evoked responses have prognostic value. Patients with minimal cortical response on MEG testing immediately following acute stroke exhibit little functional recovery and those that show a typical response pattern recover more completely. In patients with partial activation of normal cortical regions there is frequently recruitment of atypical brain areas during somatosensory, motor or language tasks.[14] Despite the involvement of other regions, this pattern of brain activation is inefficient and functional recovery is typically incomplete. A number of rehabilitative strategies have been developed, for example, intense peripheral somatosensory stimulation, immobilisation of the intact side and transcortical magnetic stimulation which may encourage further cortical plasticity and aid recovery. MEG is well suited to inform on the underlying mechanisms of rehabilitative interventions and this may, in turn, facilitate targeted therapy for individual patient populations.

Headache

There have been a number of small series studies exploring the utility of MEG in migraine. MEG field shifts and desynchronisation of alpha band activity (7-13Hz) were seen within the occipital cortex during migrainous visual auras in patients with classical migraine, consistent with cortical spreading depression.[15] Cortical hyperexcitability, determined by analysing MEG recordings during somatosensory stimulation, was demonstrated in patients with migraine compared to control subjects,[16] consistent with earlier reports of augmented visual evoked responses in this patient group. Furthermore, the degree of hyperexcitability correlated with the severity of migraine and was diminished by migraine prophylaxis with sodium valproate.[17] It may, therefore, be possible to use MEG derived markers of cortical excitability to provide surrogate evidence of the efficacy of migraine preventatives.

Multiple sclerosis

Desynchronisation within the alpha band range was also seen in patients with relapsing-remitting multiple sclerosis (MS). Interhemispheric coherence, reflecting the synchronisation between the cerebral hemispheres, was reduced in patients with MS when compared to control subjects, most likely as a result of demyelination and secondary axonal degeneration.[18] Abnormal cortical activity with an excess of slow and beta waves adjacent to subcortical white matter lesions has been identified in a small series of patients with MS,

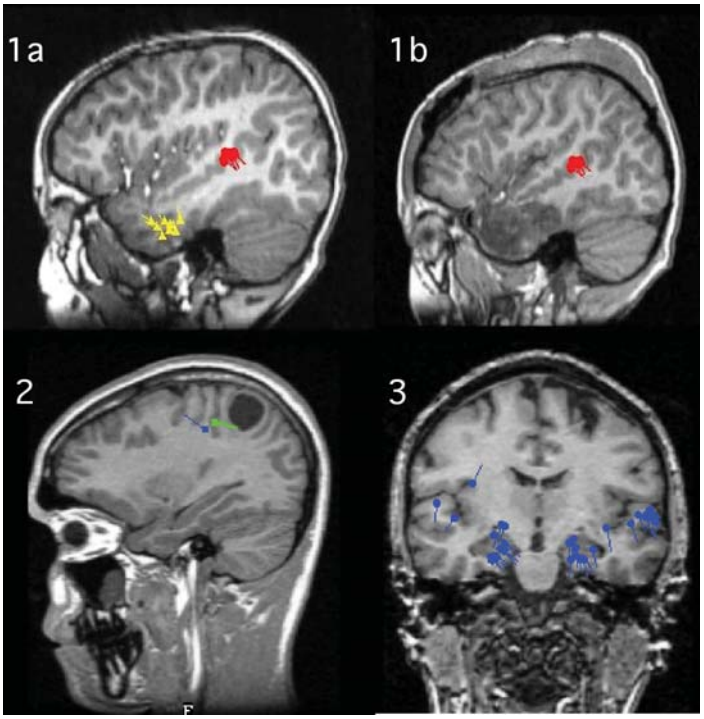


Figure 4: MEG evoked responses. 1a: pre-operative MRI with superimposed MEG derived localisation of interictal epileptiform activity (yellow triangles) and receptive language areas (red circles) in a patient with focal epilepsy undergoing pre-surgical evaluation. 1b: post-operative MRI from the same patient showing the margins of anterior temporal lobe resection and intact receptive language regions. 2: source localisation of somatosensory (green) and motor (blue) activation in a patient with a cystic parietal lobe lesion. 4: MEG-derived profiles of activation during a simultaneous auditory and visual memory task in a healthy control subject. (Images courtesy of Dr E Castillo, Division of Clinical Neurosciences, Houston).

although the significance of this remains unclear.[19] It is possible that neurophysiological parameters may provide a more sensitive marker of disease progression and treatment response than current imaging techniques such as MRI.

Future direction

MEG is an established and clinically useful technique in the investigation of patients with epilepsy. In particular, the source localisation of epileptic spikes has been validated with intracranial EEG recordings and post-operative outcome data and paradigms for the activation of somatosensory, motor and receptive language regions are reproducible and robust. The demonstration that MEG could obviate the requirement for intracranial EEG recordings or reliably guide the placement of intracranial EEG electrodes in more complex cases would be a significant advance in the presurgical evaluation of patients with drug resistant focal epilepsy. Epileptic spikes are typically seen in only 50% of interictal MEG recordings of 30-60 minutes duration. It is important therefore, to develop techniques to localise the epileptogenic zone in patients without overt interictal epileptic activity using, for example, slow waves, fast oscillations and local hypersynchrony. Paradigms for the characterisation of memory function are not yet fully established and are limited by both technical and physiological factors. Nevertheless, this is an important goal, particularly in patients with dementia for early diagnosis and treatment response or in patients undergoing epilepsy surgery. In the case of temporal lobe epilepsy surgery, the ability to localise eloquent cerebral regions and map neural networks involved in memory may lead to a more targeted / individualised surgical approach and may be able to predict and avoid post-operative memory decline.

Oscillatory synchronous rhythms are thought to coordinate large-scale neural networks, thereby influencing the perception, representation and long-term coding of information. MEG is ideally suited to explore synchrony as neither fMRI nor standard EEG are able to fully characterise the dynamic interaction between cortical regions due to limitations in temporal and spatial resolution respectively. Synchrony

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within neural networks may be disturbed in, for example, focal epilepsy, dementia or stroke and may provide useful information on prognosis and treatment response.

MEG has not yet become fully established as a routine investigation in conditions other than in epilepsy. A number of studies have suggested a specific role for MEG in, for example, stroke and cognitive impairment, but these findings need to be corroborated in larger studies before being implemented routinely. The emergence of whole head instruments with a larger number of sensors and more sophisticated analysis software is making such research more feasible, but the initial expenditure, ongoing running costs and need for experienced personnel are, for most neurological centres, prohibitive.

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Medical Treatment of Trigeminal Neuralgia

A review of the treatment of any condition must first define the diagnosis. This is by no means easy for trigeminal neuralgia (TN). Clinicians will agree that TN is a neuropathic pain syndrome characterised by brief severe lancinating pain in the trigeminal distribution of the face. These recurrent paroxysms of pain are often triggered off by direct and indirect stimuli that may be specific for individual patients. The IHS (International Headache Society) criteria for diagnosing TN is a useful definition of this condition (see Table 1).[1] However, the diagnosis is purely clinical, relying on pain descriptors and normal physical examination. Classical TN consists of painful paroxysms with little or no pain in-between each attack. Those with background pain and atypical presentation are variously known as atypical TN, TN with interparoxysmal pain (TNIP), painful trigeminal neuropathy or pretrigeminal neuralgia. Some of these conditions may merge with the syndrome of atypical facial pain.

Many patients with 'idiopathic' or primary forms of TN are found to have a loop of artery or, rarely, vein in contact with the dorsal root entry zone of the relevant trigeminal nerve. The success of microvascular decompression (MVD) in alleviating TN supports the assertion that these neurovascular contacts play a role in the pathogenesis of TN (see article by Hugh Coakham, ACNR 2007;7(2):17-18). There are also secondary forms of TN that may appear classical initially but where a plaque of demyelination, tumour or vascular malformation impinges on the trigeminal nerve. These secondary or symptomatic forms of TN may develop into 'atypical' TN with more obvious abnormal physical findings with time.

Differentiating between classical and atypical TN is important as the former is more likely to respond to MVD. This is also the case for medical treatment. Most drugs mentioned below appear to be less effective for atypical forms of TN. Making the correct diagnosis is important although response to treatment can sometimes differentiate between classical and atypical forms of TN (see Figure 1).

Assessing efficacy

Performing studies to assess therapy for TN is difficult because the condition is relatively rare and the diagnosis is dependent on clinical assessement. Spontaneous remission of TN is common and may bias both placebo and treatment effects. In addition, the pain of TN is so severe that it is difficult to justify using placebo without rescue medications. Furthermore, many medications for TN have long half lives and both therapeutic and side-effects may take time to become evident. For all these reasons, very few placebo controlled studies have been carried out for the medical treatment of TN.

Where studies are done, the main primary end points measured were pain frequency and severity. These measurements are now recognised to inadequately reflect the complex effects of chronic pain. A group of experts have formulated the IMMPACT guidelines so that future treatment efficacy should include the multi-dimensional aspects of pain.[2] The six suggested parameters to be measured in trials are: pain (severity, character, frequency, use of rescue medications), physical functioning, emotional functioning, patient global impression, adverse effects and patient disposition.

Comparing treatment effect is also difficult. Most chronic pain studies use the NNT (Number Needed to Treat) concept first proposed by Cook and Sackett in 1995. The NNT is calculated as the inverse of absolute risk reduction for any treatment. McQuay and colleagues have chosen pain relief of 50% or more as their end point.[3]

The formula for calculating NNT is:

$$\frac{1}{(N_{active}/Total_{active})-(N_{placebo}/Total_{placebo})}$$

N_{active}	Number of patients on active treatment achieving a defined end point
$Total_{active}$	Total number of patients on active treatment
$N_{placebo}$	Number of patients on placebo achieving the same defined end point
$Total_{placebo}$	Total number of patients on placebo treatment

The raw data for calculating NNT is derived from randomised placebo controlled trials and is a useful way for estimating active intervention for pain relief. However, NNTs are not directly comparable between two different trials because specific patient populations studied cannot be generalised to all patient groups. The numbers of patients studied is also crucial. The larger the number of subjects studied, the narrower the standard deviation of any NNT calculation. In spite of its imperfections, NNT measurements remain a useful concept in the comparison of different therapeutic agents for pain alleviation.

Individual drugs

Carbamazepine (CBZ)

CBZ remains the gold standard for treatment of TN. These data were derived from three placebo controlled crossover studies involving 151 patients.[4-6] The daily dose of CBZ prescribed was between 400mg-2.4g. Combining data from these studies derived a NNT of 2.6 (2.2-3.3). These three studies were reported between 1966-1969 and have never been repeated. The crossover periods were variable and in the largest study, each patient spent two periods of two weeks each on placebo and CBZ. There were also variable periods of follow-up ranging from 46 months to none. The outcomes measured included pain severity, paroxysms, triggers or pain relief. Although imperfect, this is the best published data for any medication for alleviating TN.

The side-effects of CBZ are well known to clinicians who use it for treating epilepsy. Many adverse effects are dose dependent (dizziness, sedation, diplopia, ataxia, confusion) while some are genetically linked (skin rash, Stevens-Johnson syndrome). For example, the risk of developing a cutaneous eruption with CBZ is reported to be linked to the HLA-B*1502 gene in people of Oriental descent.[7] Slow titration of carbamazepine will minimise many of its adverse effects. This is obviously not ideal for patients with TN. The starting dose is usually 100mg twice a day with increments of 100mg daily every third day until satisfactory pain relief is achieved. Checking plasma levels can be helpful and the relatively short half life means that

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Table 1: IHS Diagnostic criteria of Trigeminal Neuralgia

A. Paroxysmal attacks of pain lasting from a fraction of a second to two minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C

B. Pain has at least one of the following characteristics:

1. intense, sharp, superficial or stabbing

2. precipitated from trigger areas or by trigger factors

C. Attacks are stereotyped in the individual patient

D. There is no clinically evident neurological deficit

E. Not attributed to another disorder.

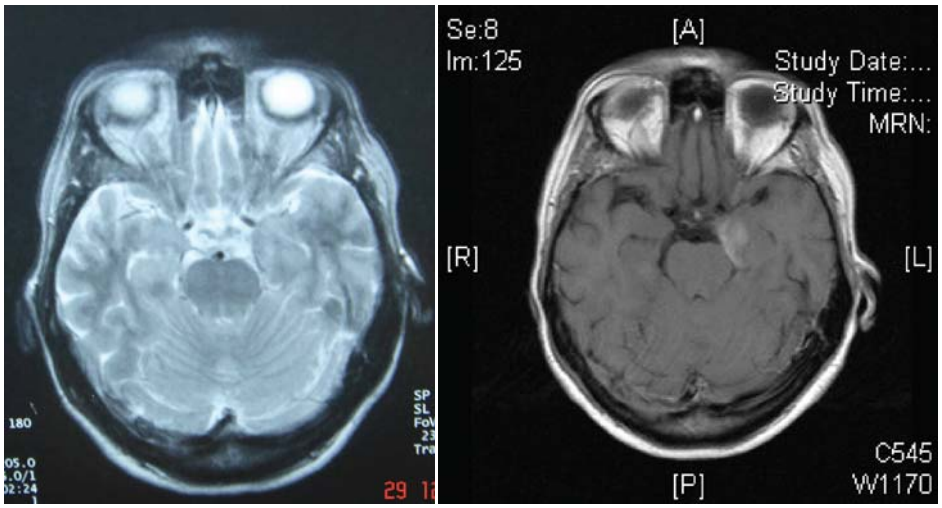

Figure 1: Atypical Trigeminal Neuralgia
This 57-year-old woman developed sharp shooting left sided facial pain with over 20 attacks an hour, each lasting for less than one minute. She experienced residual pain in-between attacks. Physical examination was normal apart from reduced sensation to light touch and pinprick over the mandibular and maxillary division of the trigeminal nerve on the left. She was diagnosed with trigeminal neuralgia initially but did not respond to carbamazepine. This diagnosis was revised to atypical TN and she subsequently achieved complete pain relieve with gabapentin. An unenhanced MRI scan done at a different hospital was reported as normal. She was seen in the Neurology clinic two years later when she developed twitching of the face. A repeat MRI scan showed this lesion in the left middle fossa consistent with a meningioma. She has undergone treatment with radiosurgery.

a steady state can be reached within three days of dose alterations. In the United States, the FDA classify CBZ in the category of a 'black box warning' drug because of its rare side-effect of causing bone marrow suppression.

Oxcarbazepine (OXC)

OXC is the 10-keto analogue of CBZ and was developed in an attempt to reduce side-effects. It has been extensively used for treating epilepsy in Scandinavia. A number of case series have reported that it may be effective for TN. The best evidence comes from three randomised double-blind multi-centred studies that compared the use of CBZ (400-1.200mg/day) versus OXC (900-2.100mg/day). A meta-analysis of these studies reported that both drugs are equally efficacious with non-significant differences in frequency of attacks or evoked pain between the two patient groups.[8] Statistically significant number of patients reported better tolerability of OXC over CBZ. This has also been reported when OXC was used to treat epilepsy. The results of these studies would argue for OXC to be used as the drug of choice for treating TN. The starting dose of OXC is 150mg twice a day and the daily dose can be increased by 300mg every three days up to a maximum of 2.4g. The serum sodium level should be monitored as OXC appear to have more of a tendency to cause hyponatraemia compared to CBZ.

Lamotrigine (LAM)

Lamotrigine is another anti-epileptic drug reported to be effective for alleviating TN. In a double blind, crossover study of 14 patients, LAM was compared to placebo as an add-on medication to either CBZ or phenytoin.[9] Total pain score, global evaluation of efficacy and use of rescue medications showed superior results in the LAM treated group compared to those on placebo. The medication is well tolerated with no patient on active treatment withdrawing from the study. Other case series have reported that LAM is effective for both idiopathic TN and that secondary to multiple sclerosis. Slow dose escalation is recommended with LAM as it has a tendency to cause severe skin reactions including a Stevens-Johnson reaction at its most extreme. For this reason, LAM is often used as an add-on with patients unresponsive or intolerant of OXC or CBZ.

Other anti-epileptic drugs

Gabapentin has a broad license in the UK as treatment for peripheral neuropathic pain. It is extensively used for alleviating post-herpetic neuralgia and painful diabetic neuropathy and is also used for treating many undiagnosed facial pains syndromes. No placebo controlled study of this medication for TN has been reported. Case studies and anecdoctal reports indicate that it is effective. The advantage of this drug is that serious side-effects are rare and it is generally well tolerated. The dose can also be rapidly escalated by 300mg daily to a maximum total dose of 1.8 to 2.4g a day.

Similarly, pregabalin has been extensively studied for treating PHN and DPN and now has a licence for treating central neuropathic pain as well. However, no placebo controlled study of this medication for TN has been reported. Whether it has any advantages over gabapentin for TN is as yet unclear.

Clonazepam was reported in a number of case series for alleviating TN. Daily doses of 2-8mg has been used but sedation is a prominent side-effect. There have not been any placebo controlled studies of this medication and it can be used for short term pain relief in patients not controlled with other medications.

A number of case series have reported that topiramate is effective for treating TN, but a small placebo controlled crossover study of only three patients has found that it is no better than placebo. The use of this medication cannot be recommended.

Phenytoin and fosphenytoin are reported in case series to be effective for TN. The advantage of these two drugs is that fosphenytoin and to a certain extent phenytoin can be administered rapidly via loading doses. However, long term use of phenytoin for treating epilepsy is on the decline due to its numerous side-effects. There are drugs with better adverse effect profiles and more evidence for efficacy than phenytoin for TN.

Sodium valproate 1.2-2g daily has also been reported to be effective for reducing the attack frequency of TN. The advantage is that valproate can be administered intravenously and achieve therapeutic serum levels quickly. However, there have not been any placebo controlled studies and long term use of this medication, particularly among the elderly, has been reported to cause extrapyramidal side-effects.

Non-antiepileptic drugs

Of the non-epileptic drugs, the best evidence is that for baclofen for alleviating TN.[10] One small placebo controlled crossover study of ten patients reported that baclofen 50-80mg daily is effective with a NNT of 1.4 (1-2.6). Baclofen has a short half life and needs to be administered three to four times a day. Most of its side-effects, like sedation, nausea, dizziness, confusion are dose dependent. Starting with 10mg three times a day, increments of 10mg daily every three days up to a maximum of 90mg daily may be used.

Pimozide and tocainide have also been reported to be effective for TN. Both of these drugs can cause cardiac arrythmias and cannot be recommended for treating TN.

Pharmacotherapy for rapid pain control

As previously described, TN pain is very severe and distressing for the patients. Medical management using anti-epileptic drugs takes time to work because of slow dose escalation necessary to avoid side-effects. Acute treatment usually consists of local anaesthetic blocks or other even more invasive procedures. One much more promising and surprising medication that may be useful for rapid alleviation of TN is subcutaneous sumatriptan. In a double blind placebo controlled crossover study of 24 patients, 3mg subcutaneously was reported to provide pain relief for up to eight hours.[11] Complete pain relief was reported by 12/24 patients on sumatriptan as opposed to none of those on placebo. A follow-on study randomised 15 patients to oral sumatriptan 50mg twice a day for one week after initial pain relief with the subcutaneous preparation.[12] Once again, sustained pain relief was reported in all patients except for two who were unable to tolerate the oral sumatriptan. In four patients who relapsed while undergoing oral treatment, a repeat injection brought about pain relief of an even greater magnitude than the first injection. Sumatriptan is a medication licensed for treating migraine and has been shown to have a wide margin of safety. It should be avoided in patients with uncontrolled hypertension and severe heart disease.

This reported efficacy of sumatriptan

Table 2: Summary of starting dose and dose escalation of medications commonly used for treating TN

Drug	Starting dose	Dose Escalation	Usual Daily Dose (Maximum)
Carbamazepine	100mg twice a day	100mg every 3 days	400-1,200mg (1.6g)
Oxcarbazepine	150mg twice a day	300mg every 3 days	600-1,800mg (2.4g)
Lamotrigine*	25mg twice a day	25mg every 3 days	100-200mg (400mg)
Gabapentin	100mg three times daily	300mg daily	1.8-2.4g (2.4g)
Baclofen*	10mg three times a day	10mg every 3 days	30-90mg (90mg)

** The starting dose and dose escalation for both lamotrigine and baclofen is faster than that recommended by the British National Formulary (BNF). The reason is because TN is such a severe pain syndrome that rapid control is necessary. If patients are unable to tolerate this rapid dose escalation, a much slower regime as recommended by the BNF can be used.*

implies that there may be an inflammatory element in the pathophysiology of TN. Sumatriptans is an agonist at 5HT1B/1D receptors co-localised in the caudal nucleus of the trigeminal nerve and trigeminal afferent terminals innervating intracranial blood vessels. Agonists at these receptors reduce neurogenic inflammation by inhibiting trigeminovascular activation, leading to the reversal of vascular dilatation and blocking the release of substance P and CGRP (Calcitonin Gene Related Protein) from afferent nerve terminals. It is unclear whether this is the mechanism of action for sumatriptan in TN. Sumatriptan has been reported to alleviate pain-fulfilling criteria for tension type headaches and even subarachnoid haemorrhage. However, another anti-inflammatory agent, the prostaglandin inhibitor misoprostol, has also been reported to alleviate TN pain secondary to multiple sclerosis. Further studies are necessary to determine whether all triptans and other compounds that block intracranial neurogenic inflammation have similar efficacy for TN.

Intranasal lignocaine was also reported to be effective for alleviating maxillary division TN in a placebo controlled crossover study.[13] Twenty five patients were randomised to 2mls of 8% lignocaine or saline. The idea was to anaesthesise the sensory and parasympathetic fibres of the maxillary division of the trigeminal nerve as it passes through the sphenopalatine fossa. Ten out of the twenty patients who were administered lignocaine reported complete alleviation of their TN. In total, 23/25 of those on active treatment reported pain relief compared to 1/25 of the patients administered saline. Stinging of the nose was common in those given active treatment, which may have unblinded the study. There was only a single cycle of treatment and it is unknown whether repeated courses will achieve the same effect. It is also unknown whether this will work in patients with TN of the ophthalmic and mandibular divisions. In spite of these limitations, intranasal ligocaine is a simple procedure with few anticipated side-effects that deserves to be assessed in larger studies.

There have been four case series of a total 16 patients reporting the benefit of botulinum toxin injections in the face for alleviating TN. Unfortunately, the diagnoses in some of these patients were not well clarified. The sites and dosage of injections vary and there is a risk of botulinum toxin causing muscle weakness when injected into the face. A properly conducted placebo controlled study is necessary to test this therapeutic option. Until then this treatment cannot be recommended for alleviating TN.

Summary

TN is a neuropathic pain syndrome characterised by severe paroxysmal facial pain. There are no pathognomonic features or tests to confirm the diagnosis and a careful clinical assessment is vital. Carbamazepine or oxcarbazepine remain the treatments of first choice for alleviating TN. Patients who are resistant or intolerant of these two medications should have a trial with gabapentin or lamotrigine. There is some evidence that baclofen and clonazepam can also help. For rapid pain control, a trial with sumatriptan is worth considering provided there are no contraindications. Surgery and microvascular decompression in particular give the best chance of long term cure but only in selected patients. Medical therapy is commonly used to control symptoms until the patients have a chance to assess their treatment options. Well designed placebo controlled studies are necessary to evaluate newer medications for alleviating TN, either alone or in combination.

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Pathology of CNS Vasculitides

This article aims to give an overview of the central nervous system (CNS) vasculitides. Vasculitides are characterised histologically by inflammation within the vessel wall itself, with or without vessel necrosis. Several classification systems have been proposed: by size of vessel affected, by mechanism of damage or, perhaps more usefully, as primary or secondary. Primary CNS vasculitis is an idiopathic disorder restricted to the CNS. Secondary CNS vasculitis occurs as part of a systemic disorder (Table 1). Exact figures for incidence rates are unavailable but primary CNS vasculitis is uncommon relative to secondary causes.

Table 1: Causes of Secondary CNS Vasculitis

Infection
Bacterial : pyogenic meningitis, TB, spirochaetes
Fungal: Aspergillus, Histoplasmosis
Parasitic: Malaria, Toxoplasma
Viral: Herpes zoster, Herpes simplex, Varicella zoster, HIV
Malignancy
Lymphoma, lymphomatoid granulomatosis
Primary Systemic Vasculitides
(See table 2)
Connective Tissue Disease
Systemic lupus erythematosus, Rheumatoid arthritis, Sjogrens disease
Drugs
Amphetamine, cocaine, vasoconstrictors
Miscellaneous
Behçets disease, sarcoidosis

Pathophysiology

In cases due to infection the infectious agent itself may directly invade the vessel wall. Most other cases have an underlying immune-mediated mechanism. Various immunopathogenic mechanisms can be involved, including immune complex deposition, cell mediated immune attack or autoantibody mediated attack. In the case of the latter there are two particular autoantibodies which are strongly associated with vascular inflammation. The first, antineutrophil cytoplasmic antibody (ANCA) is associated with various systemic vasculitides (Table 2). The other, anti-endothelial cell antibody, is directed against vascular endothelial cells in Kawasaki's disease.

The basic mechanism involves an interaction between white blood cells and the vessel wall. An initial triggering event causes circulating white blood cells and the vascular endothelium to express various cell surface markers and release a variety of pro-inflammatory soluble mediators (cytokines). This results in attachment of inflammatory cells to the vascular endothelium with subsequent migration into the vessel wall. The end result is disruption of normal vessel function with mechanical impedance to blood flow, increased vasomotor contractility and increased risk of thrombosis.[1]

Clinical presentation

The clinical presentation depends on the underlying disorder and distribution of the cerebral vessels affected. Cerebral involvement may be focal (stroke, ataxia, movement disorder, focal seizure) or non-focal (headache, encephalopathy/meningitis, psychiatric symptoms, generalised seizures). Spinal cord involvement may present as transverse myelitis/myelopathy. Other presentations include visual disturbance, mass lesion and a multiple sclerosis type picture.

Several other disorders can mimic CNS vasculitis clinically (Table 3) and should be considered in the differential diagnosis.[2,3] Evaluation of patients with suspected CNS vasculitis therefore needs to take account of both the large number of causes of secondary CNS vasculitis and the conditions that mimic it.

Useful laboratory tests include inflammatory markers (ESR/CRP), rheumatoid factor and anti-nuclear antibody for connective tissue disease; HIV, syphilis serology and blood cultures to rule out infection. CSF analysis is usually abnormal in CNS vasculitis, typically showing elevated protein levels and a lymphocytic pleocytosis. A chest X-ray is useful if sarcoid, lymphomatoid granulomatosis or malignancy is part of the differential diagnosis. No individual test has sufficient sensitivity or specificity to absolutely rule in or rule out the diagnosis.[4] The diagnostic work up should therefore aim to exclude secondary causes and mimics. If these are excluded then primary CNS vasculitis should be considered.

Since the diagnosis of a primary CNS vasculitis is one of exclusion, we shall discuss some of the secondary causes first.

Secondary causes of CNS vasculitis

Infectious agents can cause focal or diffuse vasculitis and may present with neurological manifestations in the absence of systemic disease. There is a known association between a variety of lymphomas and the occurrence of granulomatous cerebral vasculitis.

Primary systemic vasculitides are commonly classified

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Table 2: Classification of Systemic Vasculitides

	ANCA positive	***ANCA negative***
Small Vessel	*Wegener's granulomatosis* *Churg-Strauss syndrome* *Microscopic polyangiitis*	*Henoch-Schonlein purpura* *Essential cryoglobulinaemia*
Medium Vessel		*Polyarteritis nodosa* *Kawasaki disease*
Large Vessel		*Giant cell arteritis* *Takayasus's disease*

Table 3: Conditions mimicking CNS vasculitis

Cerebral Vasospasm
Migraine
Malignant systemic hypertension
Eclampsia
Phaeochromocytoma
Coagulopathies
Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Hyperviscosity syndromes (paraproteinaemia, polycythemia)
Arterial Disease
Atherosclerosis
Cerebral amyloid angiopathy
CADASIL
Moya-Moya disease
Fibromuscular dysplasia
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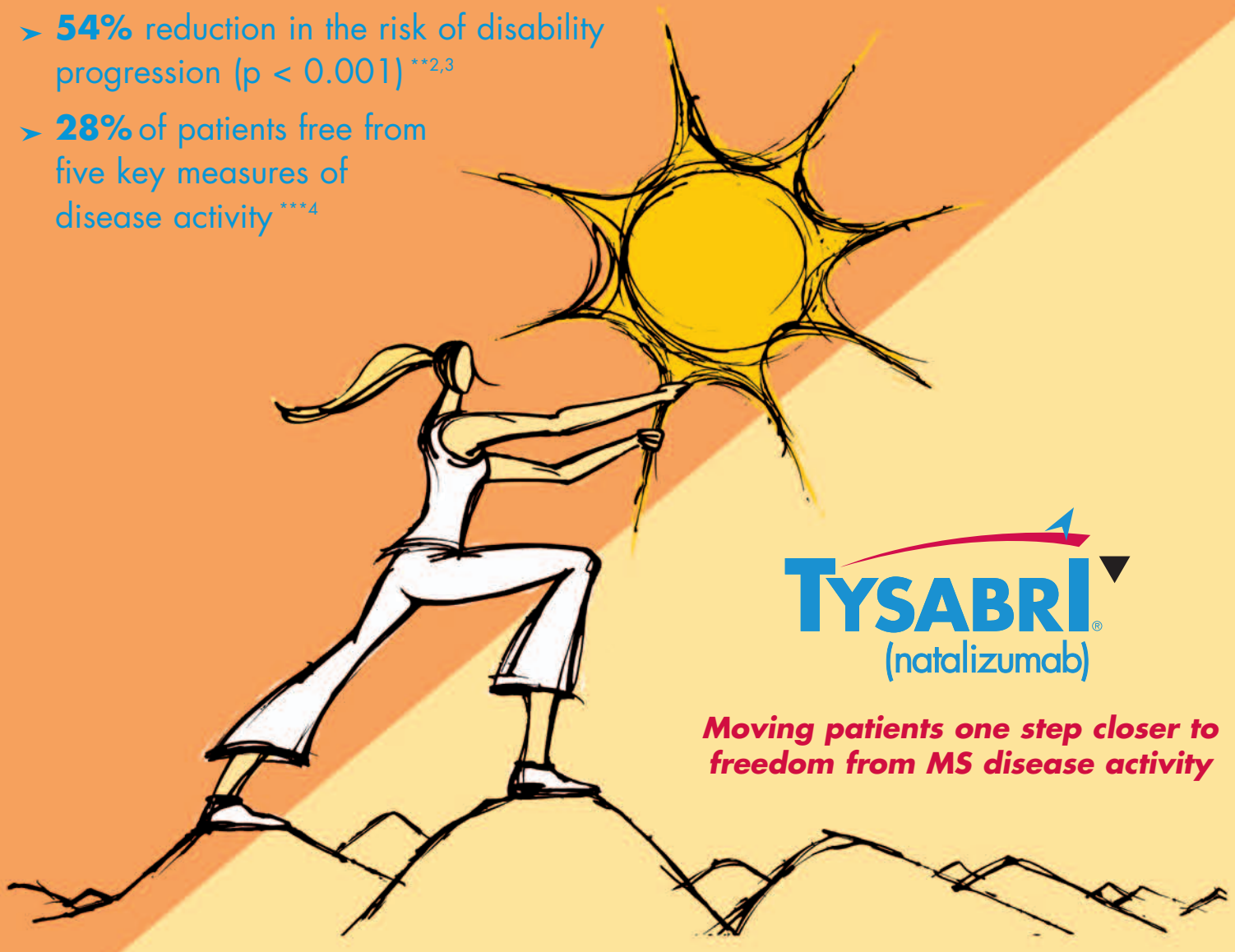

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** defined as disability progression, sustained for 24 weeks, as assessed over 2 years

*** defined as relapses, disability progression, gadolinium enchanced lesions, TI weighted hypointense and T2 weighted hyperintense lesions over two years

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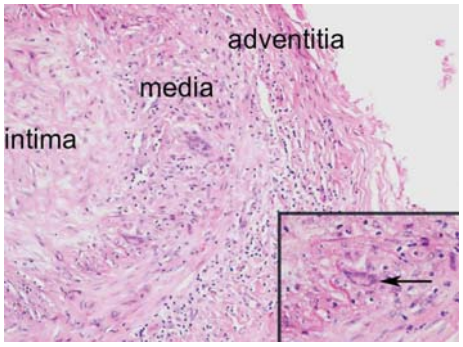


Figure 1: Giant cell arteritis: Chronic inflammatory cell infiltrate within temporal artery wall. The artery is composed of an inner endothelial layer (intima), a middle muscular layer (media), and an outer connective tissue layer (adventitia). The inflammation is centered predominantly on the internal elastic lamina (at the junction of the intima and media) and adventitia. Note the prominent intimal oedema on the left hand side of the picture (haematoxylin and eosin, x10 objective). Inset: giant cell (arrow) adjacent to pink staining fragments of disrupted internal elastic lamina (haematoxylin and eosin stain, x40 objective).

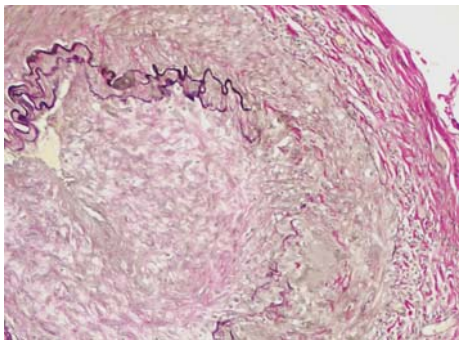


Figure 2: Giant cell arteritis: temporal artery biopsy demonstrating focal destruction of internal elastic lamina. Note the abrupt discontinuity of the black staining internal elastic lamina (elastic van Gieson stain, x10 objective).

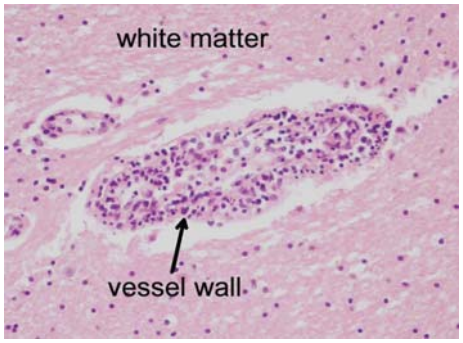
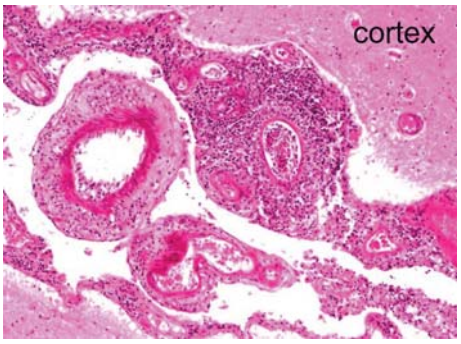
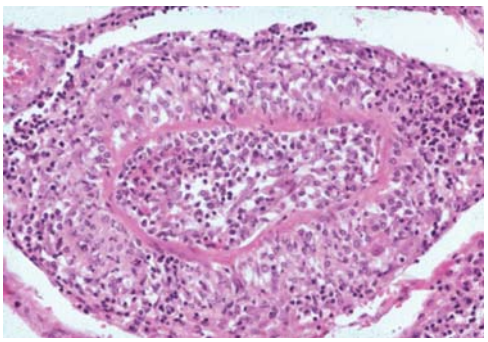


Figure 3: Cerebral systemic lupus erythematosus with a lymphocytic vasculitis - the vessel wall is expanded by a dense lymphocytic infiltrate. The surrounding tissue is cerebral white matter. (haematoxylin and eosin stain, x20 objective).

by size of vessel affected and the presence of ANCA (Table 2). Giant cell arteritis (GCA) and Takayasu's arteritis are both granulomatous primary systemic vasculitides. GCA is the more common. Both affect the aorta and its branches, GCA tending to affect the extracranial branches of the carotid, Takayasu's tending to affect the proximal branches of the aorta. The commonest cerebral manifestations of GCA are visual symptoms due to retinal ischaemia and ischaemic optic neuropathy. Temporal artery biopsy in GCA typically shows granulomatous inflammation centred on the internal elastic lamina (Figures 1 and 2). CNS involvement in Takayasu's is usually a result of carotid artery stenosis or cerebral hypoperfusion.





Figures 4 (left) and 5 (right): Primary angiitis of the central nervous system. Florid mononuclear inflammation of small meningeal arteries. The vessel walls are expanded by a variably dense infiltrate composed predominantly of lymphocytes. The surrounding tissue in figure 4 represents the underlying cerebral cortical tissue. The vessel wall in figure 5 is expanded by a dense lymphocytic infiltrate (haematoxylin and eosin stain, figure 4: x10 objective, figure 5: x20 objective).

Polyarteritis nodosa is a systemic necrotising vasculitis of medium and small vessels typically causing peripheral neuropathy. CNS involvement occurs in up to 40% of cases but is variable in its presentation. Kawasaki disease is an acute febrile multisystem vasculitis affecting medium sized vessels. It usually affects children under five years and is associated with conjunctival and oral erythema, oedema of palms and soles. CNS involvement is relatively rare. A variety of small vessel vasculitides affect the CNS and can be subclassified according to their association with ANCA. Neurological involvement is highly variable.

Several connective tissue diseases and drugs are also associated with cerebral vasculitis (Table 1 and Figure 3) but will not be discussed in further detail here.

Primary CNS vasculitis

Primary CNS vasculitis (primary angiitis of the CNS: PACNS) is a rare idiopathic vasculitis predominantly affecting small leptomeningeal vessels without evidence of systemic disease. A recent survey showed that 29 European neurologists from 15 countries collectively made a diagnosis of cerebral vasculitis in 140 patients per annum.[5] It occurs at any age but is commonest between ages 40 and 60.

Patients usually have an abnormal CSF with increased numbers of mixed chronic inflammatory cells and increased protein. MRI is usually abnormal but the features are non-specific (infarcts, leptomeningeal disease, diffuse white matter disease). Angiography is classically said to show alternating stenosis and ectasia affecting multiple vessels in multiple vascular beds. However, a wide variety of less specific findings are also described such that atheroma and vasoconstrictive disorders can mimic PACNS angiographically.

Biopsy is considered the gold standard for diagnosis (although some clinical subsets show no biopsy abnormality - see below). It is important in confirming the diagnosis and excluding other causes. In one series of biopsies for suspected PACNS alternative diagnoses requiring different management were identified in 39% of cases.[6] The serious morbidity rate associated with brain biopsy in suspected vasculitis is 3.3%, which compares favourably with that associated with the immunosuppressive treatment that a mistaken diagnosis of PACNS might entail.[7]

The main histopathological findings are chronic inflammatory cells in and around the walls of leptomeningeal and intracerebral vessels (Figures 4 and 5). The distribution is focal and segmental (explaining the angiographic appearances) and can be granulomatous, lymphocytic or mixed. Biopsy yield can be increased by sampling radiologically abnormal areas and including both leptomeninges and cortex in the sample.[8] The histological differential diagnosis includes lymphoproliferative disease, sarcoid and infection (special stains for organisms should always be performed). If the inflammatory infiltrate is predominantly lymphocytic then angiocentric lymphoma should be considered and if granulomatous then other causes of granulomatous inflammation (including tuberculosis, sarcoid and fungal infection) should be excluded.

Clinical subsets of PACNS

Increasing evidence suggests that PACNS is in fact composed of at least three differing clinical subsets with varying prognoses and treatment requirements.[9] Granulomatous angiitis of the CNS (GACNS) is the most severe form – characterised by granulomatous inflammation of small to medium vessels. CSF analysis is always abnormal but angiography may show no abnormality. Benign angiopathy of the CNS (BACNS) is a subset of PACNS which tends to follow a more benign course.[10] Angiography typically shows alternating stenosis and ectasia and these findings disappear within three to four months of symptom onset. The presentation is usually acute with focal or multi-focal neurological deficits but CSF analysis is usually normal or near normal and biopsy is negative. The aetiology is uncertain but is probably vasospastic in origin. The majority of cases fall into the grouping of "atypical PACNS". These patients fail to meet criteria for PACNS or BACNS and exhibit a lymphocytic vasculitis at biopsy. CSF analysis is typically abnormal and angiographic findings, if present, are non-reversible.

Treatment and prognosis of PACNS

No randomised trials have been performed for the treatment of PACNS. At present the usual recommendation in cases of GACNS is a regimen combining glucocorticoids plus cytotoxic drugs (usually cyclophosphamide). Response can be assessed with follow-up MRI and or

angiography. There are no specific guidelines with respect to duration of therapy but treatment is usually continued for a minimum of 6 to 12 months following remission. Atypical PACNS should be treated with glucocorticoids plus additional immunosuppressive treatment if necessary to achieve remission. Treatment of BACNS is less aggressive, usually glucocorticoids for six months, often with adjunctive calcium channel blockers.

The outcome in patients with PACNS treated with immunosuppressive treatment is less bleak than previously supposed with less than 10% mortality and approximately 20 to 30% developing significant disability.[11] Patients diagnosed with BACNS usually do well, with 94% showing significant recovery and 71% showing no evidence of long term disability.[12]

Conclusions

The central nervous vasculitides encompass a large number of primary and secondary disorders with a wide differential diagnosis. The presentation is variable and specific tests are lacking. Accurate diagnosis is important in order to exclude possible mimics which may require different therapeutic approaches and to avoid unnecessary immunosuppressive treatment with its attendant risks. There is increasing evidence that primary CNS vasculitis is composed of differing clinical subsets (on the basis of clinical, laboratory, angiographic and pathological findings) and these subsets vary in both their prognoses and treatment.

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Carphologia, or Floccillation

> Respecting the movement of the hands, I have these observations to make: when in acute fevers, pneumonia, phrenitis, or headache, the hands are waved before the face, hunting through empty space, as if gathering bits of straw, picking the nap from the coverlet, or tearing chaff from the wall – all such symptoms are bad and deadly.
> Hippocrates *Book of Prognostics* 4

Apparently aimless plucking movements have been named either carphologia or floccillation, because of their fancied likeness to picking up pieces of straw or wool, respectively. The term carphology has recently been adopted by a columnist in a rival journal,[1] but it is difficult to find any specific articles on the subject of these movements (see absence of references on Medline). Perhaps the account by Hippocrates (or his school), which I believe to be the original, said all that needs to be said. The movements have apparently been observed in dementing disorders such as Alzheimer's disease or vascular dementia, delirium (phrenitis, literally "brain fever", whence our word frenzy, may perhaps be equivalent to delirium), and some psychiatric disorders, and may possibly reflect frontal lobe dysfunction.[2] Although their description is of great antiquity, these movements may still be misinterpreted.

A 58-year-old man presented with rest and action tremor of the right (dominant) arm, slow quiet speech, hypomimia, and with examination findings of mild rigidity, micrographia, and reduced right arm swing. Concurrently, he had developed progressive memory problems sufficient to prevent him from running his business; Mini-Mental State Examination score was 19/30, with slowed responses. Neuropsychological assessment showed severe impairment on the Mattis Dementia Rating Scale, particularly on subtests of initiation/perseveration and attention, and also on the Delis-Kaplan Executive Function System, indicating a frontal-subcortical profile of dementia. Neurological signs were unresponsive to levodopa preparations. Over the subsequent two year period the patient developed progressive cognitive decline, slow saccadic eye movements, levator inhibition, retrocollis, the applause sign, and recurrent falls, on one occasion causing a fracture of the proximal phalanx of the ring finger, all felt to be consistent with a clinical diagnosis of progressive supranuclear palsy (PSP).[3]

Shortly after admission to a nursing home because of ongoing falls, care staff reported the patient to be "self-harming". Specifically, he was reported to pinch repeatedly the skin on his left arm and chest with his right arm in a rough, jerky manner, sometimes sufficiently hard to cause bruising or even draw blood. These movements were observed in the clinic as intermittent picking or plucking movements on the clothing or skin with the tremulous right hand. Patient questioning revealed no suicidal ideation or desire to self-harm.

The superimposition of a jerky action tremor on carphologia may increase the amplitude and reduce the accuracy of these otherwise innocuous movements, such that they might pinch and even break the skin, and hence be misinterpreted as self-injurious behaviour. Clearly, the identification of individuals who self-harm is of fundamental importance because of the greatly increased risk of subsequent suicide.[4] Passive self-harm in patients with dementia resident in nursing homes, such as refusal to eat, drink, or take medications, is of similar concern since this may be associated with increased mortality.[5] Self-injurious behaviour is rare in movement disorders, although it may be a feature in some (e.g. neuroacanthocytosis, Lesch-Nyhan disease). Involuntary, tremulous carphologia should not be mistaken for self-harm.

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India is a large country housing one billion people. The science of Neurology took roots in large cities of India over 50 years ago. Physicians trained in various parts of the world, in particular the UK, returned to practice neurology as a part of internal medicine in their motherland, rapidly establishing the specialty of neurology. The specialist training courses in neurology were established in the late seventies and presently, approximately one hundred neurologists are trained every year. Sub-specialty training is popular and the last decade has seen emergence of neurologists willing to work exclusively in the areas of epilepsy, strokes, movement disorders, neuromuscular diseases etc. The experience of workers in the field has suggested that the disease spectra are, in general, similar to other parts of the world; there are local peculiarities as well. This series of six parts will elucidate the patterns of neurological diseases seen in India.

Dr Khadilkar has been working in the field of neurology for over 20 years. He is Head of the Department of Neurology at the Grant Medical College and Sir JJ Group of Hospitals, Mumbai. At the Medical College, he is actively involved in teaching postgraduate students and is an examiner at the university of Mumbai for DM. in neurology.

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Headache in India

Headaches are as much a problem in India as elsewhere in the world. Given the population load, and the fact that most headaches seen in practice are underdiagnosed and undertreated, the burden of headache is significant. In this modern era, when imaging studies are easily available, most secondary headaches are identified and managed correctly. Management of secondary headaches depends on the causative factor and the strategies are the same the worldover. Amongst the secondary headaches, those due to intracranial granulomas, neurocysticercosis, meningeal infections and cerebral venous thrombosis are probably a little more common in the Indian setting.

Therefore, headache mismanagement generally pertains to primary headaches, where imaging studies are normal and investigations do not reveal an underlying cause. This article is a brief review of the Indian primary headache scene where the dilemmas are different and regional variations have an important role to play. It lists some of the more important contributions to headache literature from India.

In the light of numerous other medical problems that loom large, headache management in India is not given the priority it deserves in the health-care system. Because of limited teaching on 'headache' in medical schools and numerous additional barriers, headache diagnosis and treatment are often sub-optimal. Headache medicine is still not a recognised sub-speciality in India. Myths and misunderstandings abound and headache patients end up being seen by many different specialists, each one of whom looks at the problem through the window of their own speciality. For all these reasons, headache patients in India do not receive adequate sympathy, care and attention. Migraine is the main cause of headache burden worldwide. Even though there may not be too many variations in the clinical presentations of primary headaches across different regions of the world, treatment outcomes may vary depending on differences in genes, geography and environment. Attitudes, awareness and health-care policies all have an influence on the way headaches are perceived and managed.

India is located to the north of the equator and the heat and humidity and the numerous other migraine triggering factors all contribute to more frequent headaches that may not easily respond to medical treatment. There are many additional barriers to headache care in India. With a population of more than one billion, India has 16% of the world population and therefore health priorities keep changing. Low literacy levels make it more difficult for patients to understand the treatment plan and expectations are always high.

The health-care system in the country is also not geared to supporting effective headache treatment. Less than 5% in India seek private care or managed care. With a significant part of the population in the lower income group it is difficult for patients to seek treatment for a recurrent problem like headache. Financial constraints and fixed notions lead to poor compliance. 25% of the Indian population lives in the cities and 75% in villages. Growing urbanisation leads to infrastructural breakdown and increase in stress levels. Most of the rural population tries alternative treatment methods such as homoeopathy, ayurveda and unani. Physicians do not understand the true misery of headaches and time constraints and overcrowded clinics add to the problems of patients with headache. Headache diaries are not maintained, disability levels are not evaluated and burdens cannot be assessed.

Some important headache literature from India have been included here. There have been no standardised population based epidemiological studies that can be quoted as indicative of the true prevalence. Gowrie-Devi et al[5] did an epidemiological study of neurological disorders in Southern India which included evaluation of patients with

Figure 1: 'In the face of many other priorities…'

Having trained with Dr NH Wadia at Jaslok and then with Dr Ninan Mathew at Houston Headache Clinic, **Dr Krishnamurthy Ravishankar** is presently Consultant in charge of Headache Clinics in Mumbai. He is a member of the International Headache Society and American Headache Society and now runs an exclusive headache practice.

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Figure 2: Migraine triggers peculiar to India.

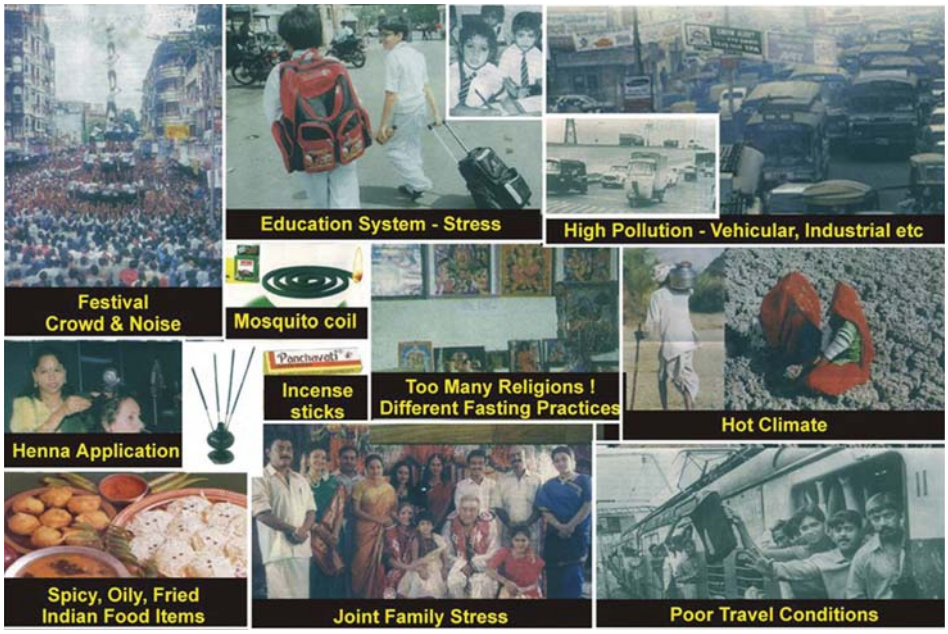

Table 1: Patient-related barriers

Myths and misconceptions
Headaches are caused by a defect in visual acuity
Headaches are caused by emotional upset
No permanent cure, so you might as well live with it
All headaches are caused by sinusitis
Headaches are caused by acidity or constipation
Delays in the seeking of treatment
Self medication
Fear of side-effects of allopathic drugs
Trial with alternative treatment options
Poor compliance
Financial constraints
Normal CT-scan results lead to the misapprehension that all is well
Inability to understand migraine
Frequent change of doctors
Poor control of triggers
Wrong levels of expectation

Table 2: Physician-related barriers

Wrong diagnosis
Low emphasis of headache in medical curriculum
Wrong treatment
Faulty drug choice
Suboptimum dose
Inadequate duration of prophylaxis
Wrong referral
Lack of effort to educate patients
Under-use of non-pharmacological strategies

Table 3: Regional barriers

Overpopulation
Low literacy
Low income
Growing urbanisation
Cultural and social diversity
Triggers peculiar to India
Inadequacies of the health-care system
Alternative therapies

headache. Ravishankar et al[1] analysed the pattern of headaches seen at a tertiary referral centre in India. Out of 1000 patients who presented with headache, 86% had primary headaches that were classifiable, 11% were unclassifiable and 3% had secondary headaches. Of the primary headaches, 55% had migraine, 28.3% had tension-type headache, 22.2% had cluster headache and 0.5% had miscellaneous primary headaches. Shah et al[2] studied 2982 patients from the Kashmir Valley and analysed the various headache patterns and cranial neuralgias. They found Ramadan fasting to be a significant factor for precipitating migraines. Shukla et al[3,4] investigated blood nitrite levels and showed that platelet aggregation response and blood nitrite levels were not significantly altered after an attack in patients with migraine. They also evaluated platelet ketanserin binding in migraine patients. Garg et al[6] have reported on patients with solitary cysticercus granuloma and seizures who also complained of disabling headache. sixteen patients with new onset disabling headache and solitary cysticercus granuloma with seizures were treated with a short course of prednisolone and obtained long lasting relief. Chakravarty A[7,8] analysed Chronic Daily Headache (CDH) in adults and children and studied the prevalence of trigemino-autonomic cephalagias (TACs)[9] seen at their centre in the eastern part of India. They found that CDH remains relatively unexplored and analgesic overuse is often not recognised. The average dose of analgesic implicated in CDH seems much less than what is reported in the West. They found that TACs are relatively uncommon in their centre.

Ravishankar[10] reported on barriers to headache care in India and the efforts that are needed to improve the situation. The barriers were grouped as patient related, physician-related and regional. Local problems that pertain to headache management, the unusual triggers seen in India and the inadequacies of the health-care system have been outlined. Besides the established triggers that are better known, Ravishankar[11] has described hair-wash or head-bath as an unusual trigger that is not seen in the West.

Panda et al[12] have reported an observational study on the clinical characteristics of migraineurs from India. They reported a low frequency of patients with a positive family history of headache. Gupta et al[13] found that 73.1% of their migraine patients had autonomic features.

Special efforts are therefore needed to tackle the headache problem in India. Awareness and education on headache needs to improve and insurance agencies must recognise headache as a valid biological disorder. We need more tertiary care clinics and lay support groups. The health care system should be modified to include headache care for all.

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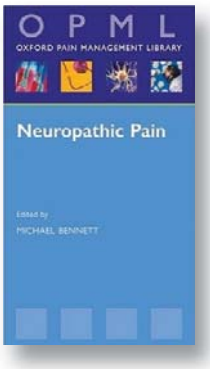
Neuropathic Pain (Oxford Pain Management Library)

This pocket book aims to be an essential guide for all those managing neuropathic pain. Its short chapters are written by British pain clinicians who provide an overview with lists of key references that can be digested in a few hours. The first section of the book outlines the epidemiology, pathophysiology, diagnosis and clinical features of the common neuropathic pain conditions. The second section covers the wide range of available treatments, including pharmacotherapy via numerous routes, neuromodulation and even acupuncture. Unfortunately the number of treatment options reflects the refractory nature of most neurogenic pain.

Neuropathic pain remains a clinical diagnosis supported by key investigations. Its definition and overlap with nociceptive pain are contentious issues that haunt the early chapters. Neurologists will need to recognise the various forms of positive sensory phenomena reflecting neuronal hyperexcitability if clinical sensory phenotypes emerge as surrogate markers for particular neuropathic mechanisms that may respond to novel drugs. The positive signs, such as mechanical and thermal allodynias, are well described here but hypodermic needles mounted in syringes are not usually used to detect altered pin prick sensation, it is impractical to test heat pain sensation using a test-tube filled with hot water and the static and pin prick forms of allodynia are not identical. David Bowsher's summary of central pain is particularly thorough and insightful. Impaired glucose tolerance was surprisingly omitted as a cause of painful sensory neuropathy and the rôle of small fibre nerve counts derived from skin biopsies could have been mentioned in the chapter on peripheral neuropathic pain. Subsequent chapters are full of valuable advice on how to use anticonvulsants, antidepressants, NMDA receptor antagonists and opioids. The chapters covering neuromodulatory techniques are packed with essential data. The available evidence base for pharmacotherapy has numerous limitations and these are explored in detail. There is an entire chapter devoted to the important topic of rational drug combination therapy which is helpfully didactic.

This book is a useful summary but contains a little repetition that is inevitable with any multi-authored text. Any criticisms are relatively minor and it is recommended as a good short introduction to neuropathic pain. Given the pharmaceutical industry's ongoing love affair with neuropathic pain I am surprised that they have not considered distributing this small, cheap book to educate a medical profession disillusioned with post-it notes and laser pens; it would certainly benefit our patients.

Gary Peters, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.



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Neurology (Oxford General Practice Library)

What should general practitioners (GPs) know about neurology? What do they need to know? How should they learn it? Considering the differing demands of medical generalism and specialism, very different answers to these questions might be suggested by GPs and neurologists, hence the joint review of this volume from the Oxford General Practice Library.

Sections are devoted to assessment, diagnosis and management of neurological conditions (including in the paediatric age group) typical of any neurological text. In addition, and of perhaps greater importance to GPs and unusual in other texts, are sections on legal aspects of care, benefits available, and the General Medical Services contract, to which there are frequent references throughout the book (e.g. for stroke, epilepsy and dementia). Other sources of information (including websites) and patient organisations (such as www.outsiders.org.uk for sexual problems in the disabled) are also listed. Accessing the appropriate agencies and resources from primary care will be facilitated by this helpful compilation. Furthermore, this text transcends the artificiality of specialty boundaries with its frequent references to other disciplines (e.g. geriatrics, mental health, pain and rehabilitation) required for optimal management of neurological disorders.

GPs and neurologists alike might wonder at some points: the inclusion of fibromyalgia (180), chronic fatigue syndrome (182), and in the paediatrics section, congenital infections (62), poor progress at school (85), hyperactivity (86) and autism (89). Would we ever think to reach for a neurology textbook to explore such issues? In contrast are omissions of certain treatment options (e.g. dopamine agonists for restless legs syndrome, botulinum toxin for spasmodic torticollis, topiramate for essential tremor). There is one definite drug error concerning steroid dosage for acute MS relapse (140), and occasional typographical errors, e.g. "Tinnel" sign (96). On carotid endarterectomy for symptomatic carotid stenosis (126), there is no evidence of benefit if <70% stenosis, not <30%, as written. Is Ménière's disease a cause of loss of consciousness (25)? A list of causes of myalgia makes no mention of polymyalgia rheumatica (22).

GPs will appreciate long forgotten neuroanatomy, summarised in six short pages, and informative sections on childhood epilepsy (76), head injury advice (112), the ABCD risk stratification of TIAs (123) (though ABCD2 is not mentioned), self-help exercises for vertigo (133) and low back pain (152), as well as important references to carer assessment (212), and the thorny issue of consent (218).

With ready access to IT based information in the consulting room, the publishers might ponder whether textbooks still have a role. Perhaps they should consider an electronic version of the OGPL series, which would sit usefully alongside other established sources, such as GP Notebook, and might reach a wider audience than the books. Nevertheless, this book has the potential to assist GPs in the management of patients with neurological disorders, it is easily portable in jacket pocket or car glove compartment, and at £5.99 it is a steal.

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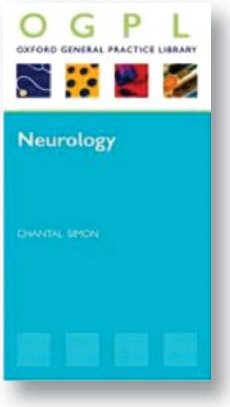

Chantal Simon
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Mea Culpa

ACNR will be introducing a series of case reports called Mea Culpa. The articles will be anonymous, to spare embarrasment, but will provide a unique means of emphasising what we can learn from our mistakes.
Are you brave enough to contribute? Contact Series Editor Stephen Kirker on stephen.kirker@addenbrookes.nhs.uk, or call 01223 217763.

Living with Traumatic Brain Injury - Carol's Voice

Steve Pape

One moment that will stay with me forever is hearing Carol's (my wife of only four months) voice for the first time. Carol had been told that there might be a possibility that I wouldn't remember who she was. Thankfully, as soon as I heard Carol's voice I knew I was safe, and I can't say how pleased Carol was to be recognised.

Something terrible must have happened for me to be in hospital. I was on a motorbiking holiday in Scotland and while riding around a left hand bend travelling at about 85mph, I lost control and crashed. I could have died on the roadside as a result of my injuries; luckily for me, I was in a group of about thirty other riders, some of whom were off duty policemen, and the first car to happen upon the crash was a nurse on her way to work. When the ambulance arrived and I was stabilised, I was taken to the nearest hospital specialising in neurological injuries, which was Ninewells Hospital in Dundee.

As time went by, I became more aware of my surroundings and that I had spent the last few weeks in a coma. I had only broken my ankle on the initial impact and the rest of my injuries were related to being thrown around like a rag doll. My helmet was shattered like an eggshell and this gave the doctors their biggest worry; it was obvious that I had sustained a serious head injury. My accident and coma had taken me back to zero; I was like a newborn baby in an adult's body.

Physically, my recovery was progressing in leaps and bounds and all my body needed was time to heal itself. There was no stopping Carol and I once I had gained some strength in my arms and legs. People think I'm joking when I tell them how badly damaged I was, but because there are no bandages or disabilities people assumed I was fully recovered.

Unfortunately, as I improved physically I slowly deteriorated mentally. Mentally, my recovery wasn't going so well. Carol and I hadn't been prepared for the effects of a head injury, we had to learn fast or there would be problems ahead. In hospital, the doctors and nurses knew how to deal with a head injury sufferer, but out in the big wide world it was a different story. This is when my frustration started to grow and I noticed that my 'anger threshold' was virtually non-existent. In the early stages of my recovery I had no self-control and no inhibitions and I could only deal with the easy, simple and small decisions and whenever I did do something, it had to be done right first time with no exception, thinking in black and white, right or wrong. This was the easy way out and required no thought at all, I wasn't concerned with the 'what if'; the 'what if' required thinking, and if it went wrong I would get annoyed with myself and anyone else who was near me. With the frustration came the depression, and I started to wear black all the time because it was easy to pick out something to wear, because black went with everything. I tried to make life as easy as possible by eliminating all the small decisions that weren't important, like what to wear. I felt like I was on train tracks heading in one direction and I couldn't get off, I was so focused on my decision, whether it was right or wrong.

I was the same person on the inside but on the outside, I came across as an angry, arrogant and difficult person. The behaviour of some family and friends towards me had changed and I was starting to be treated like an old age pensioner who couldn't take care of himself; regardless of what I said some people wouldn't take any notice of what I was telling them and only did what they thought was best; best for whom was my question, best that they were seen helping. I was starting to be treated like an object and not a person. There were many times I just wanted to scream at people because they just weren't listening to me and the less they listened, the more frustrated and angry I became. I had lost my motorbike (which was one of my passions), and people in general were treating me like an idiot. A lot of the time I did need help, but help on my terms and help that I wanted, not help that people thought I needed. I did need support and guidance, but more importantly I needed to do things for myself. I needed to learn the 'hows and whys' and I couldn't learn with people trying to help me all the time. Over a period of time I had lost my confidence and I was starting to feel like a worthless human being and no good to anyone. My frustration and anger was growing everyday and if I didn't take action to tackle it I would be in trouble.

One night Carol and I sat down and we talked about the problems I was having I had so many I didn't know which problem to tackle first. The first major problem I needed to solve was to change my working environment. At work, some of my work colleagues were taking advantage of my condition and the only decisive way to change this was to seek out new employment. This was one of the hardest decisions I had to make because I had worked for the same company for the last five years. I had worked hard and was promoted from being a worker on a production bench to a studio manager, so I was very angry at having to make this decision.

To make forward progress with my recovery, I needed to leave my past behind and find new employment. Two years had passed and I was starting my new job. I felt like I'd just climbed Mt Everest. I was so excited and I just couldn't believe what I had achieved. Both Carol and I had worked hard to get me into this position and I knew that it was all up to me now to make it work.

To show myself that I was a decent person and that I was making progress with my recovery, I sat down with a pen and paper and I wrote down everything that I had accomplished since my crash. Every little step I made was listed, starting from surviving the crash and waking up from my coma in August 2000 to starting a new job and changing my working environment in September 2002. This helped with several problems; it showed me just how much I had accomplished in the first two years after the crash. I found lots of information from various websites on the internet relating to anger management and how to control my temper when dealing with obnoxious people. Reading my accomplishment list helped with my frustration and anger but my brain was still racing ahead at full speed, my mind was like a torture device that had been programmed to destroy me.

Eventually, I found what I needed to slow my mind down: physical exercise. The more physically exhausted I became the clearer my mind became and if I kept on exercising my mind just emptied, this was what I called memory clearance. It was bliss, for the first time in months I had nothing on my mind. This was the turning point in my recovery. My confidence was increasing and my frustration and anger were becoming a thing of the past. I now accepted that things can go wrong and that I'm not perfect. It does take more effort to think about the 'what if' and thinking in black and white, right or wrong takes no effort at all. I started to realise that I had been my own worst enemy.

There tends to be a misconception that life after a brain injury is all doom and gloom. I must admit that the first year after the accident was really difficult although we received a lot of support from the various therapists at the rehab unit and from Headway, the organisation supporting brain injury sufferers and their families. I also wrote 'Stepped Off' - a book about my journey back to health, accompanied with a website (http://www.steppedoff.co.uk). The aim is to help others going through a similar experience, although no two accidents and no two-brain injuries are the same.

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 5 October, 2007

2007

September

Glial Cells in Health & Disease: VIII European Meeting
4-8 September 2007; London, UK
Laura Milne, T. 0870 143 6981,
F. 020 7808 5620,
E. info@euroglialcell.org,
www.euroglialcell.org

1st World Congress on Controversies in Neurology (CONy),
6-9 September, 2007; Berlin, Germany
E. info@comtecmed.com,
www.comtecmed.com/cony

3rd World Congress on Huntington Disease followed by the Congress of the International Huntington Association
8-12 September, 2007; Dresden, Germany
www.huntington-disease.org

2nd Neurorehabilitation Panamerican Congress
9-12 September, 2007; Buenos Aires, Argentina
E. wfnrpanam2007@congresosint.com.ar,
www.wfnrpanam2007.com.ar

British Aphasiology Society Biennial International Conference
10-12 September, 2007; Edinburgh, UK
E. louise.kelly@ed.ac.uk,
www.trainingmadeeasy.co.uk/
www.bas.org.uk

Multiple Sclerosis Trust General Study Day in MS and MND
12 September, 2007; Norwich, UK
T. 01462 476704,
E. Education@mstrust.org.uk
www.mstrust.org.uk

Pain and the Brain
12 September, 2007; Cambridge, UK
T/F. 020 8394 0400
www.physiouk.co.uk

6th International Myotonic Dystrophy Consortium Meeting
12-15 September, 2007; Milan, Italy
E. Giovanni.meola@unimi.it

3rd Mediterranean Headache School
12-16 September, 2007; Mykonos, Greece
E. one2one@ath.forthnet.gr

Practical Approaches to Working with Children & Families of Adults with Neurological Disabilities
13 September 2007, London, UK
T. 0208 780 4500 x5140,
E. institute@rhn.org.uk,
www.rhn.org.uk/institute

Parkinson's Disease - Best Practice
13 September, 2007; London, UK
T. 01722 716007,
www.mahealthcareevents.co.uk

Understanding and Treating Behaviour Problems after Brain Injury
14-15 September, 2007; London, UK
E. enquiries@braintreetraining.co.uk,
www.braintreetraining.co.uk

Congress of Neurological Surgeons Annual Meeting
15-20 September, 2007; San Diego, USA.
Congress of Neurological Surgeons.
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org,
www.neurosurgeon.org

7th Congress of the European Paediatric Neurology Society - EPNS
17-19 September, 2007; Izmir, Turkey
E. anlar@hacettepe.edu.tr

Putting Rehab into Practice – Advances
20 September, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

CRT Network Meeting 'Commissioning Rehabilitation: Practical Guidance For Service Providers'
20 September, 2007; Sheffield, UK
CRT Network Secretariat, Innervate Ltd,
T. 020 7921 0002,
E. info@innervate.co.uk,
www.p-cns.org.uk/crtconference.pdf

MS Life: Self Care, Self Management and MS
21 September, 2007; London, UK
T. 0208 438 0809,
www.mssociety.org.uk

International Clinical Trials Symposium
23-26 September, 2007; Sydney, Australia
T. +61 2 9254 5000,
F. +61 2 9251 3552,
E. info@clinicaltrials2007.com,
www.clinicaltrials2007.com

Cumberland Consensus Conference: The Future of Restorative Neuroscience in Stroke Rehabilitation
24-25 September, 2007; Windsor, UK
E. ccc@ion.ucl.ac.uk

4th World Congress of the World Institute of Pain
25-28 September, 2007; Budapest, Hungary
www.kenes.com/wip

Women with Epilepsy
26 September, 2007; Durham, UK
T. 0191 3826881,
E. Amanda.richardson@cdpct.nhs.uk

Posture & Balance in Neurological Conditions, Upper Limb Assistant Level Staff
26 September, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

International Symposium On The Vegetative And Minimally Conscious State
26-27 September, 2007; Cambridge, UK
Martin Coleman
E. mrc30@wbic.cam.ac.uk

2nd International Conference: Looking Ahead: Innovations in Brain Injury Rehabilitation
26-27 September, 2007; Leeds, UK
Frances Pitwell,
T. 01924 896100,
E. director@birt.co.uk

10th Annual Advanced Rehabilitation Course
26-28 September, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

BSRM/University of Nottingham 10th Advanced Rehabilitation Course
26-28 September, 2007; Nottingham, UK
T. ncore, 01332 254679

7th Congress Of The European Pediatric Neurology Society
26-29 September, 2007; Usadasi, Turkey
T. 90 312 454 0000,
F. 90 312 454 0001,
E. epns2007@flaptour.com.tr,
www.epns2007.org

BMJ Masterclass for Physicians: Neurology
27 September, London, UK
T. 020 7383 6985,
E. masterclasses@bmjgroup.com

Posture and Balance in Neurological Conditions, Upper Lim Qualified Staff
27-28 September, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

6th Annual Congress on Virtual Rehabilitation
27-29 September, 2007; Venice, Italy
www.aristea.com/iwvr2007

11th ILAE Specialist Registrar Teaching Weekend in Epilepsy
28-30 September, 2007; Oxford, UK
www.adoration.co.uk/ilaeform.html

MRCP Part II Course in Neurology
29-30 September, 2007; London, UK
T. 020 7692 2346,
E. j.reynolds@ion.ucl.ac.uk

October

8th Annual PDNSA National Conference
1-2 October, 2007; Birmingham, UK
E. linda.caie@nhs.net, www.pdnsa.net

Canadian League against Epilepsy - 30th Anniversary
2-4 October, 2007; Vancouver, Canada
www.clae.org

MS Course
4 October, 2007; Edinburgh, UK
T. 0131 650 8088,
E. rhona.mcdermott@nes.scot.nhs.uk

New Ways of Managing Stroke Disability
4 October, 2007; London, UK
E. carolecross@ukconnect.org
www.ukconnect.org/connectcourses_19_102.aspx

7th Annual Brain Injury Legal Seminar
4 October, 2007; Leeds, UK
Lynn Bellgard
T. 020 8780 4500 x 5161,
F. 020 8780 4530,
E. lbellgard@rhn.org.uk

ABN Joint Meeting with Indian Academy of Neurology
4-7 October, 2007; Mumbai, India
E. info@theabn.org

Neurology & Ophthalmology MRCP PACES Clinical Course
6 October, 2007; London, UK
T. 020 8292 0143,
E. neuropass@hotmail.com

132nd Annual Meeting of the American Neurological Association
7-10 October, 2007; Washington DC, USA
E. lorijanderson@msn.com,
www.aneuroa.org,

12th Pan American Congress Of Neurology
7-11 October, 2007; Santo Domingo,
Dominican Republic
E. info2007@neurocongresos.com,
www.kenes.com/neuro-congresos/

Prague07 – Living with MS: Today and Tomorrow
10 October, 2007; Prague, Czech Republic
E. info@msif.org,
www.prague07.net

MS Academia - Multiple Sclerosis Advanced Course 2007
10 October, 2007; Prague, Czech Republic
www.seronosymposia.org/en/Neurology/
...page.html

The International League Against Epilepsy (UK Chapter) Annual Scientific Meeting
10-12 October, 2007; Southhampton
www.conference2k.com

4th ISPRM World Congress, Seoul, Korea
8-12, October 2007; Seoul, Korea
E. traceymole@wfnr.co.uk

MS Academia - Multiple Sclerosis Advanced Course 2007
10 October, 2007; Prague, Czech Republic
E. info@seronosymposia.org
www.seronosymposia.org/en/Neurology/
Symposia/MSAcademia07/page.html

2nd International Symposium on Brain, Vision and Artificial intelligence - BVAI 2007
10-12 October, 2007; Naples, Italy
E. bvai2007@biocib.cib.na.cnr.it

Parkinson's Disease Foundation's 50th Anniversary Conference: Frontiers of Science and Clinical Advances in Quality of Life
11-12 October, 2007; New York, NY, USA
E. info@pdf.org, www.pdf.org

ECTRIMS 2007
11-14 October, 2007; Prague, Czech Republic
Prof. Eva Havrdová
T. +420 22 496 55 46,
F. +420 22 491 79 07,
E. ehavr@lf1.cuni.cz

British Society for Clinical Neurophysiology Scientific Meeting & AGM
12 October, 2007; London, UK
Tel. 0207 601 8859,
E. bscnsecretariat@btinternet.com

Training Day for Acquired Brain Injury
12 October, 2007; Dartmouth, UK
Tel. 01803 834 921,
E. jmaddison@dartmouthcollege.devon.sch.uk

4th International Meeting of The Brain Stem Society
12-13 October, 2007; Mainz, Germany
Dr. Jürgen Marx,
T. +49-6131-177194,
F. +49-6131-175697,
E. marx@neurologie.klinik.uni-mainz.de

British Society of Neuroradiology Annual Meeting
12-13 October, 2007; London, UK
www.bsnr.co.uk

European College of Neuropsychopharmacology 20th Conference
13-17 October 2007; Vienna, Austria
T. +49 30 300 669 0,
F. +49 30 300 669 50,
E. ecnp@congrex.nl, www.ecnp.nl/

International Psychogeriatric Association 13th Congress
14-18 October, 2007; Osaka, Japan
E. ipa@ipa-online.org

BNA Symposium: Bench to Bedside in Acute Stroke
17 October, 2007; Edinburgh, UK
www.bna.org.uk/edinburgh_oneday.htm

Consent to Treatment fully incorporating the mental Capacity Act
17 October, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

AANEM Annual Scientific Meetings
17-20 October, 2007; Phoenix, Arizona, USA
AANEM
T. + (507) 288-0100,
F. + (507) 288-1225,
E. aanem@aanem.org

Exploring Gait as it relates to Posture and Balance for qualified therapists
18 October, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

Neurodrug 2007
23-25 October, 2007; London, UK
T. 0207 539 4336,
E. julie.phillips@Terrapinn.com

International Symposium Syringomyelia 2007
23-26 October, 2007; Rugby, UK
E. admin@syringomyelia.org

Headway Annual Conference
22 October, 2007; Stratford, UK
Rachel Broughton,
T. 0115 924 0800.

Understanding Brain Injury
26 October, 2007; Ely, UK
T. 01353 652176

European Society of Gene and Cell Therapy Annual Congress 2007
27-30 October, 2007; Rotterdam, Netherlands
Karina Lööw,
T. 46 84 596 600,
F. 46 86 619 125,
E. esgct@congrex.com

Parkinson's Plus Study Day
29 October, 2007; Derby, UK
T. 01332 254679,
E. ncore@derbyhospitals.nhs.uk,
www.ncore.org.uk

STARS Conference
29-31 October, 2007; Birmingham, UK
www.heartrhythm.org.uk

The Ketogenic Diet Conference 2007

Keto PAG

Ketogenic Professional Advisory Group

THIS IS A MUST ATTEND EVENT FOR ALL NEUROLOGISTS, DIETITIANS AND EPILEPSY SPECIALIST NURSES - BOTH ADULT AND PAEDIATRIC.

There will be Lectures, networking and open discussions on the latest, exciting developments and practice from the world's leading experts, led by Professor Helen Cross from GOSH.

15th and 16th November 2007
Copthorne Effingham Park Hotel
Nr Gatwick, RH10 3EU.
UK.

Accreditation applied for and there are strictly limited places so please ensure you register as soon as possible.

For Further Information and Booking Details please visit *www.matthewsfriends.org* or contact Emma Williams – 0788 4054811 or Julie Edwards – 0774 8800438, alternatively email *enq@matthewsfriends.org*

Hosted by

MATTHEWS FRIENDS
The Ketogenic Diet
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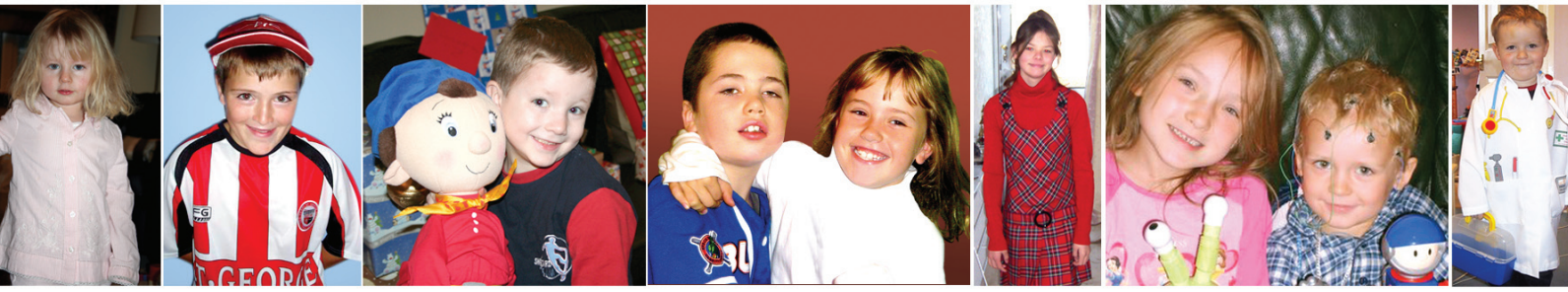

17th Meeting of the European Neurological Society

16-20 June 2007; Rhodes, Greece

The 17th annual meeting of the European Neurological Society took place over five days and was attended by around 2800 delegates from over 71 countries. The setting of Rhodes was lovely for both the conference and some relaxation as the conference venue was big and well organised, with Greek bars, restaurants and the beach within easy reach for the evenings.

Throughout the event, 23 teaching courses covered a wide spectrum of mainstream topics such as "Dementia" or "Parkinson's Disease", and were usually run by national experts in their field. The ENS thus provides a chance to attend a multitude of courses in an international setting within a short period of time. As the speakers often originated from several different countries, cohesion between individual presentations was sometimes lacking, and the short course duration of half a day dictated that topics could not be covered exhaustively. However, they ran in a friendly environment and the audience was actively encouraged to participate. A particular highlight was the newly-introduced course "How to write a scientific paper and grant application", in which Professor Brandt, co-chief editor of the Journal of Neurology, gave practical and humorous insights into his editing work. In addition to providing many helpful tips on improving one's chances of acceptance, he illustrated them by discussing the rationale for acceptance or rejection of past submissions.

Several symposia were interspersed among the teaching courses, covering issues as diverse as axonal protection in chronic inflammatory demyelinating disease and stroke prevention. The symposium on mitochondrial disorders was particularly well attended and provided complimentary lectures with direct relevance to the practising clinician.

Almost 600 posters were presented. Due to the acceptance rate of 80%, overall standards were high. As an interesting novelty, posters were published on a USB stick.

One of the excellent elements of the conference was the Young Neurologist in Training programme, which offered grants to 300 European trainee neurologists. These cover accommodation, conference registration and attendance at three teaching courses. This is a superb way to support trainees in attending such a conference, particularly in the current climate where when one of the authors (GPW) has had all study leave funding withdrawn. Sadly, only 13 UK trainees made use of this opportunity in 2007.

Overall, the large size of the conference and number of sessions offered meant that there was something for everyone regardless of their interests. Despite the size, the organisation was good, although occasionally marred by technical issues with the voting system and multiple speakers being flummoxed by the audiovisual equipment. Delegates came from a wide range of different backgrounds, including a significant younger contingent supported by the Young Neurologist grants, enabling networking. The great diversity of the sessions and the delegates, coupled with the setting in Rhodes, made for a very enjoyable and rewarding conference.

Next year's conference marks the 20th anniversary of the ENS. Like the inaugural meeting, it will be held in Nice, France, and hopefully the size of the UK contingent will start to reflect this country's leading role in neurology.

Stephan Jaiser, Newcastle General Hospital, Newcastle upon Tyne.
Gavin Winston, National Hospital for Neurology & Neurosurgery, London.

Data Presented at the ENS

The topics covered at the ENS were numerous. This selection gives some insight into the data presented:

Multiple Sclerosis: Experts emphasised that too much time is lost from the manifestation of the first symptom to the determination of diagnosis. Studies performed in patients after the first attack of the disease suggest that beta interferons display greater efficacy when used in the early phase of disease. Other immune-modulating substances should also be administered as early as possible.

Stroke: Stroke disease is the third most common cause of death and the most common cause of severe disability for adults in industrialised countries. Studies reported at the meeting indicated that aspirin reduces the risk of myocardial infarction in men, but not stroke; the opposite is true in women. In addition, surgical procedures to prevent stroke pose a greater risk to women. Early diagnosis and efficient treatment of depression can achieve better results in rehabilitation. Using transcranial Direct Current Stimulation (tDCS) and also Transcranial Magnet Stimulation (TMS) to influence regions of the brain responsible for language could help to improve aphasia in stroke patients.

Frontotemporal Dementia (FTD): 10-20% of all dementia cases are caused by FTD. Researchers reported that since dementia is often only associated with forgetfulness people affected by this disorder suffer for a long time before correct diagnosis is made. Patients frequently lose their ability to adapt to social situations first.

Heavy Intake of Alcohol: Constant alcohol consumption results not only in cognitive disorders but can elicit symptoms of frank dementia in people as young as in their forties, as presented by neurologists from the University of Medicine in Gdansk, Poland. The individuals examined had an alcohol dependency averaging 20 years. Of the total, 25.9 percent definitely suffered from anxiety disorders and another 18.5 percent probably did, while 7.4 percent definitely suffered from depression and a further 7.4 percent probably did, regardless of the individuals' age and duration of addiction. The test results indicated that a further 14.8 percent had test scores below the limit at which cognitive disorders can be excluded. Their memory, use of language and/or orientation all showed deficits. Experts demanded more public education about the consequences and dangers of alcohol abuse.

ENS Administrative Secretariat.

8th International Stereotactic Radiosurgery Congress

San Francisco, US, 23-27 June, 2007.

The Palace Hotel, located in the centre of downtown San Francisco provided a superb venue for the 8th ISRS Conference. The congress provides a multi-disciplinary forum for all those working in the Stereotactic Radiosurgery field. Not surprisingly the largest groups of delegates were neurosurgeons, oncologists and medical physicists. The local organising committee should be congratulated for orchestrating a well-balanced programme covering all aspects of Stereotactic Radiosurgery. Breakfast sessions were well attended and plenary lectures were delivered to a packed auditorium.

Stereotactic Radiosurgery is not empowered with large multi-centred randomised controlled trials. However Aoyama et al. presented results from the Japanese trial assigning patients with metastatic brain tumours to receive whole brain radiotherapy plus SRS or SRS alone. He reported that there was no difference in survival between the two groups, but that intracranial relapse was more common in the SRS group alone.

Numerous large series of patients with AVM's, acoustic neuromas, skull-based meningiomas and metastases were presented from well established units. Refinements in techniques such as tractography and intensity modulated radiosurgery aiming to minimise collateral damage and maximise the success of treatments was discussed. The use of fractionation was also considered as a strategy to try and reduce side effects. The quality of discussion was of a very high standard without exception.

The broadening of Stereotactic Radiosurgery to patients harbouring other lesions, such as cavernomas and gliomas was also reviewed. The preliminary data on glioma management is very interesting and almost certainly warrants a revisit of an SRS approach to the treatment of these cases.

The best poster award was presented to Mitsuya Koichi from Japan for his perfusion MR imaging techniques to help distinguish tumour recurrence from radiation necrosis. Stereotactic Body Radiation Therapy is an emerging technique. This was recognised by the presentation of the Young Investigator Award to Vanessa Panettieri from Spain for her modelling studies on the delivery of radiation to lung tumours in collaboration with the Karolinska University Hospital Unit.

Douglas Kondziolka, a dynamic and talented neurosurgeon from Pittsburgh was awarded the Fabrikant Medal. He delivered a brilliant lecture providing an overview of 8,000 SRS patients treated in his unit. He covered the technological advances in radiosurgery, the principles of treatment and the principles of management of patients with a large variety of intra-cranial conditions. This talk was undoubtedly the highlight of the academic programme.

This well organised conference was attended by specialists from all over the world and encouraged the dissemination of emerging technologies in a convivial atmosphere. The 8th ISRS Congress is due to be held in Seoul. I do hope that the organisers use the academic blueprint from the San Francisco meeting to help organise an equally successful meeting.

Peter Whitfield, South West Stereotactic Radiosurgery Centre.

PREVIEW: International Conference on the Dietary Treatments for Epilepsy

West Sussex, UK, 15-16 November, 2007.

'KetoPAG' (Ketogenic Professional Advisory Group) are a group of professionals working with the ketogenic diet. They aim to promote good practice, education and support in promotion of the use of the ketogenic diet in the treatment of epilepsy.

On 15th and 16th November 2007, at the Copthorne Effingham Park Hotel, Nr Gatwick, West Sussex, KetoPAG present an International Conference on the Dietary Treatments for Epilepsy.

The conference aims to bring together multi-disciplinary professionals involved in the use of the ketogenic diet, with an international faculty updating on the latest evidence for use; Helen Cross, Professor and Honorary Consultant in Paediatric Neurology, with a special interest in complex epilepsy at Institute of Child Health & Great Ormond Street Hospital for Children will update on their recently completed randomised controlled trial evaluating the efficacy of the ketogenic diet.

Mechanisms of action, multicultural use and different diets that could be used, as well as specific roles for the diet outside epilepsy, are among the topics covered by a distinguished faculty, who include; Dr Eric Kossoff, Associate Professor of Paediatrics & Neurology, Johns Hopkins, Baltimore, USA; Dr Jong Rho, Director of Paediatric Epilepsy Research, The Barrow Neurological Institute, Phoenix, Arizona, USA; Dr Jorg Klepper, Paediatric Neurologist Ascaffenburg, Germany; Dr Janek Nathan, Paediatric Neurologist Mumbai, India and Dr Ruth Williams, Paediatric Neurologist, Evelina Children's Hospital, London UK.

There will also be practical-based workshops for education and sharing of experiences. KetoPAG are pleased to be working with Matthew's Friends, the UK charity for the ketogenic diet, who are hosting this conference on their behalf. Emma Williams, Founder and Chief Executive of Matthew's Friends and also the Parent Representative on KetoPAG, along with her team, will be pleased to accept bookings via www.matthewsfriends.org and also poster submissions. All enquiries in the first instance to enq@matthewsfriends.org.

PREVIEW: MS Society Professional Network Conference

The MS Society is hosting its Professional Network Conference, entitled 'Self care, self management and MS' at the British Library in London on Friday 21st September.

This year's MS Society Professional Network conference tackles the theme of self care and self management – an issue very much in the news right now and one that looks set to shape the future of health and social care.

Key speakers will set out the principles and policy and leading practitioners together with self-management volunteers will discuss the practical implementation.

The conference includes ample opportunity to network with other professionals. There is no charge for this event but you do need to book your place. Programmes with booking forms are available on the MS website at www.mssociety.org.uk

Join the Professional Network
The MS Professional Network is a multi-disciplinary network to promote good practice in MS care.
Over 2,000 health and social care professionals have already joined. If you are interested in improving services for people with MS then join now. It costs nothing and you can join by going to www.mssociety.org.uk/profs

PREVIEW: Clinical Update: Epilepsy in Adults and Adolescents

This meeting of the The Royal Society of Medicine takes place on Friday 9 November from 9.15am – 5.10 pm, in London.

The meeting aims to provide an update on some important issues of diagnosis and treatment for people with epilepsy. Some of the social and employment consequences of epilepsy will also be considered. The focus of the conference is to take a practical approach, and the programme is intended particularly for all those working in epilepsy clinics, general physicians and general practitioners, and also for general neurologists and trainees.

For more information and to register on-line please visit
http://www.rsm.ac.uk/academ/e10-2-epilepsy.php
or contact Tori Bennett T. 020 7290 3856, F. 020 7290 2989,
E. tori.bennett@rsm.ac.uk

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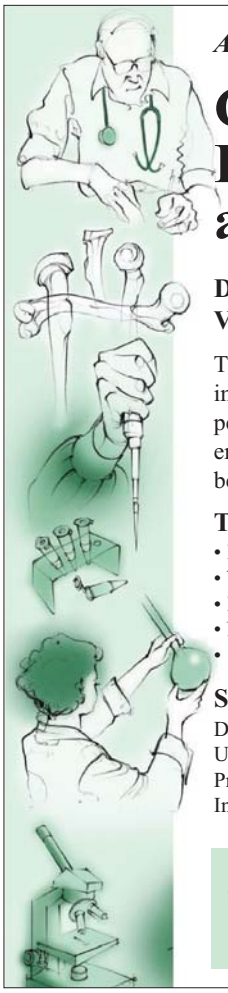

A Royal Society of Medicine Symposium

Clinical Update: Epilepsy in adults and adolescents

Date - Friday 9 November 2007
Venue - The Royal Society of Medicine

This meeting aims to provide an update on some important issues of diagnosis and treatment for people with epilepsy. Some of the social and employment consequences of epilepsy will also be considered.

Topics include:

- Diagnosis, differential diagnosis and investigation
- When should treatment be started?
- Living with epilepsy
- Non-epileptic attack disorder (NEAD)
- Shard decision making in epilepsy

Speakers will include:

Dr Philip Smith,
University Hospital of Wales, Cardiff
Professor Simon Shorvon,
Institute of Neurology

For more information or a booking form, please contact **Saheeda Rahman** on **0207 290 3844**. You can also book online at **www.rsm.ac.uk/diary**

The Royal Society of Medicine

THE BRITISH NEUROPSYCHIATRY ASSOCIATION

BNPA
British Neuropsychiatry Association

www.bnpa.org.uk
7/8 FEBRUARY 2008
The Institute of Child Health, Guilford Street, London

PROVISIONAL PROGRAMME

Thursday 7th February
ANGER AND VIOLENCE: NEUROBIOLOGY AND MANAGEMENT.
Plus Members' Papers

Thursday am
0930-1030 PLENARY - Cognitive Neuroscience of psychopathy - James Blair (USA)
1100-1125 Risk assessment and management of aggression – Thomas Fahy (UK)
1130-1155 Episodic and impulsive disorders of aggression following head trauma – Rodger Ll Wood (UK)
1200-1225 Epilepsy and aggression – Rod Duncan (UK)
Thursday pm Members' Papers

BNPA Guest Lecture
1600-1700 Brain mechanisms, moral decision-making and antisocial behaviour - Adrian Raine (USA)
BNPA RECEPTION – THE WESTMINSTER BOATING BASE

Friday 8th February
PAIN/PLACEBO. Plus BNPA 2008 AGM and Members' Papers

Friday am
0930-0955 Headache and management - Peter Goadsby (UK)
1000-1025 Pain a clinical perspective - Charlotte Feinman (UK)
1100-1125 Psychological Management of Chronic Pain - Amanda Williams (UK)
1130-1155 Pain and Neuroimaging - Predrag Petrovic (Sweden)
Friday pm Members' Papers

EVOLUTION OF THE HUMAN MIND
1430-1455 The basics of human evolution - Chris Stringer (UK)
1500-1525 The evolution of human society - Robin Dunbar (UK)
1530-1555 The evolution of mind-reading - Simon Baron-Cohen (UK)
1600 Prize giving
1615 Tea and Close

EUROPEAN CHARCOT FOUNDATION
UNIVERSITY CLASSES IV

Focussed on Progressive MS

An educational programme on Multiple Sclerosis

November 28, 2007, Fiuggi, Italy

Faculty:

M.P. Amato, W. Brück, M. Clanet, G. Comi, G. Ebers, G. Edan, F. Fazekas, O. Fernandez, S. Fredrikson, N.E. Gilhus, H.-P. Hartung, J. Palace, B. Uitdehaag

Call for Biogen Idec young investigators travel grants

The European Charcot Foundation is pleased to announce that Biogen Idec has provided an unrestricted educational grant to sponsor 20 young investigators with a travel grant of € 1000,- to attend the University Classes in Multiple Sclerosis IV.

Young investigators are invited to apply before October 15, 2007. Conditions for applications are available on our website.

EUROPEAN CHARCOT FOUNDATION
SYMPOSIUM

Treatment Targets in Multiple Sclerosis
'The ends and the means'

November 29, 30 and December 1, 2007, Fiuggi, Italy

13th European Charcot Foundation Lecture

Prof. L. Steinman
'New targets of treatment in Multiple Sclerosis'

Sessions on:

- Targets for treatment of Multiple Sclerosis
- B and T cell activities in MS
- The blood-brain barrier and inflammation
- Compartmentalization of inflammation in the CNS in Multiple Sclerosis
- Brain tissue injury
- How to measure treatment effects in MS?

For detailed information and registration visit our website www.charcot-ms.eu

Glatiramer Acetate (Copaxone®) in Multiple Sclerosis

Multiple sclerosis (MS) is the most common, non-traumatic, disabling neurological disorder in young adults. Although the aetiology of MS remains unknown, its pathogenesis includes an inflammatory demyelinating process with immune reactivity to antigens such as myelin components, and progressive neuronal and axonal damage.

The clinical course of relapsing remitting MS (RRMS) is punctuated by exacerbations or episodic neurological worsening. These attacks, or relapses, are followed within weeks to a few months by remissions, often with full recovery from clinical symptoms. However, recovery from some relapses can be incomplete, resulting in increased impairment and disability.[1] However, it is during the later progressive phase that the majority of the permanent disability is acquired. The impact of MS on the individual is variable but uncertainty is a constant feature which adds an extra psychological burden.

Management must be tailored to the individual patient in order to cope with the ongoing variability of the condition. In addition to treating acute relapses and managing clinical symptoms, disease modifying therapies (DMTs) are prescribed to decrease relapse frequency. This will have a direct effect on function but in addition there is the hope that reducing inflammation will lead over the longer-term to a reduction in subsequent neurodegeneration and disability.

Key aims of MS treatment currently include:

- Managing the wide and varied range of clinical symptoms and associated problems
- Treating active inflammatory disease i.e. acute relapses
- Disease modification: reducing/preventing future relapses and reducing disability
- Encouraging adherence to treatment in order to maximise the efficacy

The availability of disease modifying therapies (DMTs) for the treatment of MS in the 1990s represented a major step forward in the management of MS. These agents are currently considered to represent the best disease modifying therapeutic options for the treatment of RRMS.

Glatiramer acetate (Copaxone® – subcutaneous) and the other disease modifying drugs licensed for RRMS, interferon beta-1b (Betaferon® - subcutaneous) and interferon beta-1a (Avonex® - intramuscular; Rebif® - subcutaneous) have been shown to decrease relapse rate, increase the proportion of relapse-free individuals, decrease frequency of new enhancing lesions on magnetic resonance imaging (MRI) and decrease accumulating T2 MRI lesions burden.[2] This article will review the evidence and latest developments with glatiramer acetate (GA), one of the currently approved DMTs for RRMS.

What is glatiramer acetate?

Glatiramer acetate is a non-steroidal and non-interferon DMT. Its mode of action, which is based on its similarity to natural myelin, is different to that of interferon beta and other anti-inflammatory drugs used in MS. Previously referred to as copolymer-1 (Cop-1), it is made up of randomly assembled synthetic polypeptides composed of the four major amino acids found in the basic protein of myelin: L-alanine, L-glutamic acid, L-lysine and L-tyrosine.

The full mechanism of action of GA in humans still has some uncertainty attached. Possible processes include facilitating a shift to a less pro-inflammatory immune response, tolerance of a myelin response, or a broader neurotrophic effect.[3]

Dr Jacqueline Palace is a Consultant Neurologist with a special interest in multiple sclerosis. She is also an Honorary Senior Lecturer at Oxford University and Co-ordinator for the Department of Health Risk Sharing Scheme for disease modifying drugs in multiple sclerosis. Dr Palace currently runs an MS clinical service in Oxford.

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Clinical trials with glatiramer acetate

The first double-blind, randomised, placebo-controlled trial of GA in patients with RRMS was conducted in the US in the 1980s. Results showed the proportion of relapse-free patients was significantly higher in the GA-treated cohort compared to the placebo group (56% vs. 26%; p=0.045). The overall two-year relapse frequencies were 0.6 and 2.7 in the GA and placebo groups, respectively. The mean unconfirmed improvement on the Kurtzke Disability Status Scale (DSS) was 0.5 units with GA, whereas those taking placebo worsened by an average of 1.2 DSS units (p=0.012).[4]

A pivotal US multi-centre study of patients with RRMS, with two or more relapses in the two years before enrolment, showed a relapse rate at 24 months of 1.19 + 0.13 for those treated with GA compared to 1.68 + 0.13 for the placebo group, a 29% reduction in favour of GA (p=0.007); annualised rates were 0.59 and 0.84, respectively.[5] The proportion of patients who improved, were unchanged or worsened by > 1 point on the expanded disability status scale (EDSS) at the end of two years, also favoured GA (p=0.037),[5] although sustained disability was not reduced over the two years. At the end of a blinded extension phase (extended by a mean of 5.2 months in the GA and 5.9 months in the placebo arm) there was a 32% reduction in mean relapse rate with GA (1.34 for GA and 1.98 for placebo, p=0.002), with annualised relapse rates of 0.58 and 0.81, respectively. During the entire extended trial, 33.6% and 24.6% of GA -versus placebo-treated patients remained relapse-free, respectively (p=0.035).[6]

Continuous open label prospective follow-up of this study is ongoing.[7] Of the original 251 patients, 208 chose to continue in the follow-up study and were all given GA. The annualised relapse rate of patients treated from the beginning of the study dropped each year. Of the 152 patients followed at almost six years of continuous treatment with glatiramer acetate since trial entry, 25.7% remained relapse free.[8] The mean annualised relapse rate of over six years for those who received GA from randomisation was 0.42 (95% CI=0.34-0.51), a 72% decrease compared with their pre-study rate.[9] Of those treated with the agent from study inception, 69.3% were either neurologically unchanged (within 0.5 EDSS units of baseline) or had improved by at least one unit on the EDSS.[8]

At eight years, 56.6% of the original patients remained in the study.[10] The annual relapse rate had declined to 0.2.[10] The mean EDSS for the entire cohort was 3.14, which represents an increase of 0.55 units from randomisation.[10] Patients treated with glatiramer acetate continuously for the entire ten-year study period showed better outcomes than those switched from placebo to GA which has led to the suggestion that earlier treatment may be more beneficial in the long-term.[11] However, it is difficult to draw conclusions from the extension phase due to factors such as regression towards the mean, the natural history of relapse rate reduction over time and patients continuing on treatment being unrepresentative of the total group.[8] Indeed the GA from onset arm who entered the open label phase progressed in disability and relapsed less during the double blind phase than those who did not continue in the study. A similar bias in relapse frequency and in disability progression was seen in the placebo at onset group;[8] for disability progression however the bias in this group was not statistically significant.[8]

Magnetic resonance imaging (MRI) studies provide a non-invasive estimate of some of the pathological changes in the central nervous system (CNS). MRI studies have shown that GA can reduce the number of new enhancing lesions,[12] decrease volume of enhancing lesions,[12] reduces the number of recently formed new lesions[12] and reduces the proportion of new lesions that develop into permanent black holes.[13] Further data have shown an improvement in NAA:Creatinine ratios in patients treated with GA suggesting neuro-axonal recovery in MS patients.[14]

Combination therapy

Interferon beta and GA have different mechanisms of action, so it is reasonable to consider combination therapy. In vitro studies have shown both drugs have a greater effect on reducing the proliferation of myelin basic protein (MBP) -specific T cells than either drug alone.[15] A small 12-month study of combination therapy with interferon beta -1a and GA showed that the combination was well tolerated and statistically significant improvements in the MSFC at six months and walking time at 12 months were demonstrated.[16] A larger trial has been funded through the National Institute of Health to further explore these initial observations.

Tolerability

The long-term tolerability and safety of GA was investigated in patients with RRMS with over a

Publication of this article has been made possible by an educational grant from Teva Pharmaceuticals Ltd.

decade of continuous use, with injection site reactions being the most common adverse effect.[7] Immediate Post-Injection Reactions are described, which include one or more symptoms from vasodilatation, tachycardia, chest pain, dyspnoea or palpitations. These are short-lived, resolve spontaneously and do not persist over time.[17] No time dependent adverse effects were observed and there was no evidence of haematological, hepatic or renal dysfunction, emergence of malignancy or development of other autoimmune diseases.[7] Of 124 withdrawals from the ongoing, prospective study 23 were due to adverse events, 27 to patient perception of disease worsening and 22 to patient desire to switch or combine therapies. The remainder included reasons such as pregnancy or difficulty or unwillingness to adhere to the study protocol.[7] The readiness of the 108 (46%) ongoing patients to continue the use of GA after ten years indicates the tolerability and safety of the drug.[7] With long-term use, regular injections can result in skin changes, including lipoatrophy.[17] These are usually mild[17] and can be reduced and managed by good injection practice.

Glatiramer acetate in clinical practice

Glatiramer acetate is indicated for the reduction in frequency of relapses in ambulatory patients with RRMS characterised by at least two attacks of neurological dysfunction over the preceding two-year period.[17] When the National Institute for Clinical Excellence (NICE) reviewed GA and interferon beta for use by the NHS the cost-effectiveness analyses obtained from the short-term data did not reach the required threshold. It was advised that DMTs be prescribed in a cost-effective manner to NHS patients and thus the 'risk sharing' agreement between the pharmaceutical companies and the Department of Health was set up. This scheme makes DMTs available to eligible patients on condition that the disability change is monitored in a cohort over ten years and that a target of £36,000 per QALY should be met over a twenty year projection - if necessary with price adjustment of the treatment.[18]

Under the risk sharing scheme, patients with RRMS who meet the 2001 criteria developed by the Association of British Neurologists, are eligible for NHS funded treatment.[19] These guidelines state that patients can be offered GA provided that they have RRMS; can walk 100 metres or more without assistance; have had at least two clinically significant relapses in the past two years; are aged 18 years or older and do not have contraindications. The scheme recommends that any of the drugs should be stopped if patients suffer intolerable side-effects; become pregnant or are planning pregnancy; suffer two disabling relapses within a 12-month period; develop secondary progressive MS or lose the ability to walk, with or without assistance, for longer than six months.[19]

Interferon beta is associated with the development of neutralising antibodies (NAbs) and the proportion of patients varies according to the specific formulation prescribed. Recently published guidelines from the European Federation of Neurological Societies (EFNS) on the use and relevance of NAb measurements, recommend that tests for the presence of NAbs should be performed on all patients treated with interferon beta at 12 and 24 months, positive tests should be reconfirmed after 3-6 months and patients who have persistently high levels of neutralising antibodies should have their interferon beta therapy discontinued.[20] Switching to GA is clearly still an option if these patients remain eligible. GA binding antibodies are common in patients on GA. Binding antibodies have not been shown to have an effect on disability or side-effects and there may even be a beneficial influence on relapses.[21] It should be noted that because the efficacy of GA is likely to be related to its activation of immune mechanisms the production of antibodies may theoretically be beneficial.

A recent study demonstrated that prior treatment with interferon beta-1b does not reduce the efficacy or affect the tolerability of GA.[2] The prospective, open-label study evaluated the efficacy of GA in a group of patients previously treated with interferon beta-1b (n=247) and a group of treatment-naïve patients (n=558). Results showed that annual relapse rates declined by about 75% in both cohorts.[2] The researchers concluded that switching to GA could benefit patients who discontinue interferon beta therapy.

There is also growing interest in the use of DMTs in combination with short-term anti-inflammatory agents to treat patients with highly active forms of MS. Mitoxantrone (an immunosuppressant usually used to treat cancer, which has been approved for use in MS in the US) has previously been shown to reduce relapses in MS,[22] but its long-term use is limited by its potential toxicity.[23] Previous attempts to extend its effectiveness with subsequent use of interferon beta have shown a deterioration in three out of ten patients.[24] In a recent observational study a combination of a limited course of mitoxantrone was overlapped with and followed by long-term GA in a consecutive series of 27 patients. The rapid reduction in relapse activity observed following the initiation of mitoxantrone was successfully maintained by the use of GA as a follow-up treatment. Results showed a sustained 90% reduction in annualised relapse rate ($p<0.001$), falling from 2.7 to 0.106 relapses per year, which has been maintained for a mean of 36 months in follow-up so far.[25] The combination therapy improved, or at least stabilised, existing levels of disability in the 27 patients taking part in the study, as measured by both clinical and MRI criteria. Thus the option of follow on therapy with GA appears to be promising.

Conclusion

MS is a chronic disabling disease. Although the immunopharmacology of GA is complex and not yet completely understood, it represents a useful and well-tolerated DMT for patients with RRMS. In addition, the lack of a requirement for routine blood test monitoring makes it a valuable option in practice. Glatiramer acetate offers an attractive first line therapy in the treatment of patients with RRMS and is the logical alternative for patients who are not responding adequately to interferon beta or who develop interferon beta NAbs, and for those who suffer intolerable side-effects. The use of GA in combination with other immunosuppressive treatments looks promising for the future.

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The views expressed are the author's own. Dr Palace received no remuneration for this editorial.

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The Francis Crick Lecturer 2007 - Professor Geraint Rees

Professor Geraint Rees (Wellcome Trust Centre for Neuroimaging at UCL and the UCL Institute of Cognitive Neuroscience) has been awarded the Royal Society's Francis Crick Lectureship for 2007.

The Francis Crick Lecture was established in 2003 following an endowment by Dr Sydney Brenner CH FRS, joint winner of the 2002 Nobel Prize in Physiology or Medicine. The prize lecture is delivered each year in any field of the Biological Sciences, but preference is given to the areas in which Francis Crick himself worked: genetics, molecular biology and neurobiology. Fundamental theoretical work, which was the hallmark of Crick's science, will also be given preference. Importantly, the lectureship is aimed at younger scientists. Ideally, nominees should be under the age of 40, but the intention is that the lecture will be awarded to someone whose career stage corresponds to under 40, thus making allowance for people whose career progression may have followed a less routine or more interrupted path.

Nominations for the Francis Crick Lecture will reopen on 1 December 2007. See www.royalsoc.ac.uk for more information

Epilepsy award

A health award which recognises the efforts of individuals and teams trying to develop better healthcare for the half a million people with epilepsy in the UK and Ireland was launched recently. The BEST (Best Epilepsy Standards Today) award, an initiative of the Joint Epilepsy Council (JEC), aims to raise awareness of the condition and to encourage epilepsy service improvements. Nominations for the award can be made by patients or their family members, voluntary groups and volunteers, primary practice and specialist nurses, health visitors, GPs and pharmacists. Entries can come from health students, administrators, community or hospital healthcare teams and consultants working in England, Northern Ireland, Republic of Ireland, Scotland and Wales.

See www.jointepilepsycouncil.org.uk for details. Deadline for nominations is September 7, 2007.

ENS Fellowship Stipend 2008

If you have an experimental project in neurology of your own design and would like to carry it out in the near future, apply now for an ENS Fellowship for the year 2008. The second deadline for this stipend is October 15, 2007.

The European Neurological Society will support the scholarship holder for a period of 6 months, with a monthly stipend of EUR 2,000. The scholarship is to be held at a host institution in Europe during the year 2008. ENS sponsors this programme to provide an opportunity for talented researchers to participate in an exchange of scientific activities between home and host institutions. Programme is primarily aimed at young

Applicants must be less than 40 years of age, and affiliated with an academic neurological department. Applicants and / or home or host institution must be active at ENS meetings. The ENS invites applicants from European nations, as well as those outside Europe.

Application forms can be obtained from the web site www.ensinfo.com

Epilepsy Research News

In April 2007, the Epilepsy Research Foundation merged with the Fund for Epilepsy, creating Epilepsy Research UK. Epilepsy Research UK is the only charity dedicated to funding independent epilepsy research in the UK. There are 28 grants ongoing, representing a total commitment of £1,300,000 to epilepsy research. The Epilepsy Research Foundation made five new research project grants in 2006/7, totalling £322,816.

Bruno Frenguelli and Nicholas Dale of the University of Warwick were awarded £69,950 to investigate the regulation of cortical excitability and seizure activity by purines.

John Jefferys and colleagues at the University of Birmingham received £74,932 for a combined in vitro and in vivo study of Fast network activity and neuronal aggregate formation preceding epileptic seizures. Precursor work to this project was also funded by the Epilepsy Research Foundation.

A total of £79,997 was awarded to Dr Frances Platt and colleagues at University of Oxford and St George's Hospital Medical School for a study of Human GM3 synthase deficiency, a new severe epilepsy syndrome (co-funded with The Wellcome Trust).

The effect of status epilepticus-induced neuroinflammation on brain injury and epileptogenesis will be studied by Rod Scott, Mark Lythgoe and colleagues at UCL Institute of Child Health and Institute of Neurology, who were awarded £79,937.

Professor Adam Zeman and colleagues at the Peninsula Medical School, Exeter will investigate the impairment of memory in epilepsy: the significance of autobiographical amnesia. This is an Economic and Social Research Council CASE Studentship; the Epilepsy Research Foundation will contribute £18,000.

For more information see www.epilepsyresearch.org.uk

13th European Charcot Foundation Lecture

The European Charcot Foundation Annual Symposium 2007 takes place November 29-30 and December 1 in Fiuggi (Italy): "Treatment Targets in Multiple Sclerosis. The ends and the means". Prof. L. Steinman will open the Symposium with the 13th European Charcot Foundation Lecture.

The three-day Symposium will discuss treatment perspectives at various levels of the immune system (periphery, blood brain barrier and brain compartment). In this way a coherent view of available and prospective treatments can be given. The Symposium is preceded by "University Classes in Multiple Sclerosis IV", a teaching course focused on progressive MS, on November 28, 2007 at the same venue.

Participants of the course are updated on the latest developments in the field by a prominent faculty of European MS researchers. The course is directed at general neurologists, neurologists in training, rehabilitation specialists, urologists, ophthalmologists, MS investigators and pharma staff.

Biogen Idec Travel Grants are available for neurologists in training and young MS researchers to support participation in this course. For more information see www.charcot-ms.eu

Epilepsy Action have in recent years funded several important projects...

Epilepsy Action is committed. In recent years they have funded several important projects and developed a number of funding initiatives including postgraduate research bursaries, studentships and prizes.

Epilepsy Action has now launched a new programme of research awards worth more than £100,000 each year. This will incorporate existing awards and introduce new large and small scale grants and PhD studentships for research into the causes and cures of epilepsy. Researchers and students working within the British Isles, including Eire, will be eligible to apply to for Epilepsy Action Research Grants Programme funding.

Further information can be found on Epilepsy Action's website www.epilepsy.org.uk/research/awards.html or contact Margaret Rawnsley on Tel. +44 (0)113 210 8800, E. reseach@epilepsy.org.uk

EDITOR'S CHOICE

MULTIPLE SCLEROSIS: controversial benefit of the interferons

In the world of multiple sclerosis, all is not quiet. A new study, reported recently in the Lancet, has generated new hope for people with multiple sclerosis and their doctors, exercised commentators, brought a smile to the MRI industry and induced migraine in health care accountants. And it has given a new twist to a debate amongst UK neurologists about the latest Association of British Neurologists document on the use of interferons.[1] You may remember Professor Scolding's robust critique of the ABN's recommendations in the "controversies" section of the last issue of ACNR.[2]

The Big Question is this: should people who have had a first attack of demyelination (the "clinically isolated syndrome") be started on beta-interferon? Three trials have now addressed this issue, called CHAMPS, ETOMS and BENEFIT.[3-5] The results of these have led some neurologists to adopt wholesale the policy of interferon for all clinically isolated syndromes, some to advocate treatment only when there are MRI abnormalities, and some to argue that there is good evidence NOT to put such people on interferons. These discrepant interpretations of the trials arise from disagreement about what is a real and useful marker of the efficacy of interferon treatment of the clinically isolated syndrome.

Perhaps you think that it is important that the risk of a second episode of demyelination is reduced? After all, this would mean that the "conversion" to a clinical diagnosis of multiple sclerosis is delayed. Put like that, it sounds pretty impressive. If that is what you are after, then interferon is for you. All trials have focused on those "high-risk" patients who present with a clinically isolated syndrome and some MRI abnormalities that looked like demyelination. The risk of such people developing clinically definite multiple sclerosis over 14 years is 90% (and only 20% for those with normal MRI scans). The data from all three trials are very consistent: over two to three years beta-interferon reduces the conversion rate to multiple sclerosis from 45-50% on placebo to 28-35% if you take interferon-beta. Excellent.

The trouble is that some fussy people, of whom I am one, insist that the key measure of interferon treatment of the clinically isolated syndrome is whether or not it reduces the accumulation of disability in the long-term. Here the trial data are poorly disclosed, messy and terribly complicated. The bottom line is that no effect on disability was seen in the ETOMS trial or the CHAMPS original- and five year extension- trial. And now comes along the BENEFIT trial which reports that early beta-interferon treatment of the clinically isolated syndrome of demyelination reduces the risk of accumulating fixed disability over three years by 40%.

What to make of these conflicting results? Without doubt, the most robust and sophisticated of the three trials is the BENEFIT study and its data on disability are probably the most reliable. However, it is not a straightforward trial at all. In fact, I think it is one of the most tortuous trial designs of any I have seen in multiple sclerosis. I suspect the root problem was that the sponsors and investigators were not confident they would see an effect on disability. So they hedged their bets with three primary efficacy measures, tested one after the other in a "sequential conditional" analysis. The first step was examining the effect on conversion to multiple sclerosis in a two-year trial of placebo (n=176) versus beta-interferon (n=292) in people with a clinically isolated syndrome and a minimum of two clinically silent MRI lesions.[5] From this came the replication of ETOMS and CHAMPS. The second step was a pre-planned extension study for one further year looking at the accumulation of disability at three years. The trouble is that at the end of the two-year placebo-controlled trial, all patients were offered beta-interferon for a further year, so the groups now consisted of those patients who had been on beta-interferon all the time (early treatment) or those originally randomised to placebo who had changed to interferon either at two years or earlier if they had developed clinically definite multiple sclerosis (delayed treatment). Because a statistically significant result emerged, the BENEFIT trialists allowed themselves a third analysis of disability with the "functional assessment of multiple sclerosis trials outcome score". Are you keeping up?

As you would expect, not many people accumulated fixed disability during the three years on the BENEFIT study. After all, these are basically well people at the earliest stage of multiple sclerosis. The numbers hitting the disability marker were 42/292 from the early group and 40/176 in the delayed treatment arm. From these figures emerges the "40% reduction in risk of disability" headline. Another way of expressing the same data is the number needed to treat with interferon early, rather than late, to avoid one person acquiring fixed disability over three years is 12.

This is an important result. After all, any reduction in the risk of disability in young, well, productive people should be welcomed with open arms. Remember that multiple sclerosis is a serious disease; it is associated with disability, depression, reduced employment, increased divorce and a shortened life-span. It is easy to lose one's head over this and allow the rhetoric to flow, either too strenuously supporting or knocking such results. As Joseph Addison (1672 - 1719) said "make perseverance your bosom friend, experience your wise counsellor, caution your elder brother, and hope your guardian genius". In that spirit, I would advocate hopeful caution about the BENEFIT trial. The disability result is not sufficiently robust to change practice for two reasons. Firstly, it is based on events in just 82 patients and 68 of the patients who started the trial were lost to analysis at three years. In other words there is missing data from nearly as many people as those whose events contributed to the headline result. The impact of this was formally studied by a "sensitivity analysis", by factoring a worst or best case scenario for the missing data; the significance of the disability result did not survive such an analysis. Secondly, the positive result on disability as measured by the EDSS was an isolated finding. All of the other disability-related outcome measures, both clinical and radiological, were not significantly different between early and late treatment.

So where does this leave the ABN recommendations? Which were, to remind you, that interferons are started at the time of the "diagnosis of MS by the McDonald criteria within one year of presentation with a clinically isolated syndrome (CIS) typical for MS". As the text and references clearly show, these recommendations were written by people who are impressed by the action of interferons on reducing the conversion rate of clinically isolated syndromes; and not at all concerned whether they have an effect on disability (which the report does not even mention). Hence the vulnerability of the guidelines to criticism. Now, with the subsequent publication of the BENEFIT trial, the author's may feel vindicated after the fact. Perhaps so. But it remains an unusual way to have gone about writing a document intended to inform regular neurological practice.

In the end, we have to decide whether BENEFIT is sufficiently robust to radically alter our approach to clinically isolated syndromes. I suggest not. Not because the trial was poorly performed or badly analysed, but it was just too complicated and too small. As with many of our commentaries on trials in ACNR we end by saying we need another trial, bigger and simpler, to be sure of the benefit that BENEFIT promises. - ***AJC***

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Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study.
LANCET
2007 Aug 4;370(9585):389-97.

HEADACHE: Valproate for chronic headache

This open, retrospective study looked at the use of divalproex sodium (sodium valproate) in the long-term treatment of chronic headache. Other studies, both controlled and open-labelled have shown short-term efficacy, but this study looked at efficacy and tolerability over six years in 642 patients. The standard index, 50% reduction in headache frequency, was achieved in 75% of the 138 patients receiving only divalproex as headache prophylaxis. Adverse events occurred in 35%, and none were severe. Weight gain in this study was minor, and counter to the experience in patients with epilepsy, occurred less in women than men (men mean 7 lbs, women 1.9 lbs). This study is not first-rank evidence, but long term and extension studies like this provide very important information about practical use. This study adds evidence for the use of valproate in treatment of chronic headache, a difficult area often muddied by analgesia overuse. So, although it is not going to be chosen for women of active child-bearing potential, valproate is another useful medicine for chronic migraine. - ***HAL***

Freitag FG, Diamond S, Diamond ML, Urban GJ.
Divalproex in the long term treatment of chronic daily headache.
HEADACHE
2007;41:271-8.

PARKINSON'S DISEASE: Pacemakers and pathogenesis

★★★ RECOMMENDED

One of the major issues in neurodegenerative disorders of the CNS is why specific population of neurons should be selectively vulnerable. One recent hypothesis to explain this in Parkinson's disease involves a change in the ionic basis of pacemaking activity in neurons in the substantia nigra dopaminergic neurons. These neurons have an intrinsic pacemaker activity that in the adult is driven by a proximally located L type calcium channel, which in turn has an effect on a calcium activated potassium channel. In addition there are cyclic nucleotide gated cation channels within nigral cells which also work in conjunction with the calcium influx to mediate pacemaker activity. In the juvenile substantia nigra however sodium channels and influx drives pacemaker activity instead of the calcium channel although the process can be recapitulated in the adult if the calcium channel is blocked. So how does this help in our understanding of the regional pathology in Parkinson's disease? The answer may be that this relatively unique population of substantia nigra dopaminergic cells uses large calcium currents for pacemaker activity which means they can easily be stressed because they are subject to large calcium influxes.

The next question that follows is: if these neurons are so vulnerable why is it that only a proportion of people get Parkinson's disease when presumably everyone expresses this calcium channel? The answer to this may lie in some subtle genetic variability. For example, PINK1, one genetic cause of parkinsonism, affects mitochondrial function which is intimately linked to oxidative stress and the intracellular handling of calcium. So will this lead to the treatment of Parkinson's disease with calcium channel blockers? Maybe, but the dose, selectivity and side effect profile of such therapies at the present time argues against their use although this study by Chan et al is certainly thought provoking and offers an exciting new avenue for treatment in Parkinson's disease.

A second paper in Nature is also of great interest in the field of Parkinson's disease as it reports on the discovery of a new trophic factor for dopaminergic nigral neurons called Conserved Dopamine Neurotrophic Factor or CDNF. This factor is described in detail and is shown to protect and rescue dopaminergic function in vivo in the face of neurotoxic insults to the nigrostriatal tract using 6 hydroxy dopamine. Indeed this factor unlike GDNF seems to demonstrate great specificity of action for nigral dopaminergic neurons, even though its distribution is not exclusively in this system. Thus we have a new neurotrophic factor which may have a potential role in the genesis and/or treatment of Parkinson's disease. I wonder what effect this factor has on the pacemaking nigral neurons and Parkinson's disease? - ***RAB***

Chan CS, Guzman JN, Ilijic E, Mercer JN, Rick C, Tkatch T, Meredith GE, Surmeier DJ.
Rejuvenation' protects neurons in mouse models of Parkinson's disease.
NATURE
2007; 447:1081-1087.

Lindholm P, Voutilainen MH, Lauren J, Peranen J, Leppanen VM, Andressoo JO, Lindahl M, Janhunen S, Kalkkinen N, Timmusk T, Tuominen RK, Saarma M.
Novel neurotrophic factor CDNF protects and rescues midbrain dopamine enurons in vivo.
NATURE
2007; 448:73-78.

BRAIN INJURY: and mobile phones

★★★ RECOMMENDED

Having a functional memory is fundamental to the ability to participate in everyday life. Memory loss is one of the common cognitive sequelae of traumatic brain injury and the "rehabilitation" of memory problems can be seen by non-specialists as an esoteric and, perhaps, optimistic pursuit. A recent review, cited in this paper, defines the differences between compensatory and restorative techniques in the management of post-traumatic memory disorders and the lack of good evidence for the efficacy of restorative techniques. What, then, of compensatory strategies in the clinical rehabilitation of memory deficits? While we are all familiar with the use of a diaries and whiteboards, more sophisticated external prompts, such as the Neuropage system pioneered by Barbara Wilson and her group are (far from routinely) available to assist those in the community who require regular prompts throughout the day for specific activities. Since the development of these devices, the mobile 'phone has become a ubiquitous part of life for an ever increasing number of people in the developed world. Although modern 'phones can have a bewildering array of features, they are relatively inexpensive in comparison with Neuropage type systems. The authors of this study, therefore, looked to assess the value of the "reminders" function in a small group of patients with post brain injury memory problems as a compensatory cognitive aid. A set of "target behaviours" were agreed between the patient and carer which were important activities which the patient would be able to engage in independently and would usually forget to do. The number of times that these behaviours were carried out (indicating memory success) was recorded over a seven week period with- and without pre-recorded prompts set on a mobile 'phone for these activities. Perhaps, disappointingly only 2 out of 5 patients recruited demonstrated an improvement in target behaviours with the 'phone. The 3 patients who did not, apparently, benefit all required 24 hour care whereas the 2 patients who showed an increase in target behaviours were not in receipt of a 24 hour care regime. This would suggest that the external memory prompt is likely to prove more useful in patients with a higher functional level. Although this is a small pilot study, it does highlight the potential contribution of everyday technology as a cost-effective aid to the management of memory deficits which is certainly to be welcomed given the paucity of options currently available for this patient group. ***-LB***

Stapleton S, Adams M, Atterton L.
A mobile phone as a memory aid for individuals with traumatic brain injury: a preliminary investigation.
BRAIN INJURY
2007; 21(4):401-11.

HUNTINGTON'S DISEASE: and disgust

Many studies examining emotion recognition have suggested that detection of disgust relies on processing within the basal ganglia and insula. Patients with Huntington's disease, a disease that has as part of its core pathology basal ganglia atrophy, have in the past been shown to have a relative impairment in recognising disgust. In this recent study this has now been extended and better defined, as Johnson et al have examined emotion recognition in 475 affected HD patients and 57 individuals without the pathological HD CAG expansion. The study visit included a 3 hour cognitive assessment, a neurological examination, structural MRI, blood sampling, medical history and assessments of psychiatric/ behavioural status using questionnaires as part of the PREDICT-HD study. Inclusion criteria required that all participants had undergone genetic testing and were found to have a CAG expansion in the HD gene. The clinical examination included the UHDRS (Unified Huntington's Disease Rating Scale), ANART (American National Adult Reading Test) - an estimate of general intellectual functioning - BDI (Beck depression inventory), a self report on current symptoms of depression. Structural magnetic resonance imaging was undertaken and volumetric analyses of the caudate nucleus and putamen were carried out. In addition, all the patients completed the Benton Facial Recognition task and the emotion recognition task as part of a larger cognitive assessment battery where the disgust scale was again part of a self report questionnaire. The main result from this study indicated that recognition of all negative emotions declines early in the disease process and that there seems to be a poorer performance when individuals are close to expressing symptoms of the disease. Furthermore, in contrast to other studies there appears to be deficit in recognising disgust in presymptomatic HD and patients and there is no evidence to support a direct link between the striatal atrophy and disgust recognition. Thus given the power of such a large study with well-characterised individuals, it seems that a deficit in the recognition of disgust is not a robust finding in HD individuals, at least in those in the presymptomatic stage of the disorder. However, longitudinal data is still needed before any final conclusions can be

made of this issue. In addition, since there is no relationship between changes in striatal volume and recognition of disgust or any other emotion this suggests that volumetric changes in the striatum are not responsible for changes in emotion recognition. - *CA*

Johnson A, Stout J, Solomon A, Langbehn D, Aylward E, Cruce C, Ross C, Nance M, Kayson E, Julian – Baros E, Hayden M, Kieburtz K, Guttman M, Oakes D, Shoulson I, Belinger L, Duff K, Penziner E, Paulsen J and the Predict – HD investigators of and the Huntington Study Group.

Beyond disgust: impaired recognition of negative emotions prior to diagnosis in Huntington's disease.

BRAIN

2007;130:1732-44.

HEADACHE: Mechanisms of trigeminal ganglion signalling

Activation of trigeminal ganglion nerves and release of calcitonin gene-related peptide (CRGP) are implicated in the development of migraine. This study examined the neuronal-glia interactions within the trigeminal ganglion during normal and inflammatory conditions, in rats. A retrograde tracer was used to localise the cell bodies in the ganglion and studies conducted during basal conditions and after injection of capsaicin into the temporomandibular joint capsule, used as a noxious stimulus to the third division of the trigeminal. The position of the tracer and levels of CGRP and cytokines were measured under control and activated conditions. Under conditions of stimulation, there was tracer present in surrounding glia, and therefore communication between the neuronal-glia gap junctions. Further there was increased expression of inflammatory proteins in all divisions of the trigeminal ganglion, not just the third division which had been stimulated. This study showed in an experimental model that noxious stimulation of one division of the trigeminal resulted in activation of neuronal-glial gap junctions and set up an inflammatory cascade which involved a wider anatomical area, namely all three divisions of the trigeminal. While caution is needed in extrapolation to migraine in humans, this research is important because it highlights some of the possible mechanisms for the initiation of migraine and sensitisation of surrounding areas. – *HAL*

Thalakoti S, Patil VV, Damodaram S, Vause CV, Langford LE, Freeman SE, Durham PL.

Neuron-glia signalling in trigeminal ganglion: implications for migraine pathology.

HEADACHE

2007;47:1008-23.

BELL'S PALSY: Smile but not too much, it's the quality of smile that counts

★★★ RECOMMENDED

People with Bell's palsy are often treated using a combination of exercises and electrical stimulation of facial muscles. The exercises will typically include smiles, eye closures, eye brow raises, frowns, mouth puckers and pouts, as well as tasks such as using a straw, blowing up balloons and chewing gum on the affected side. The electric stimulation serves to increase the afferent input through lots of repeated contractions of facial muscles. Although improvement occurs, some patients fail to develop the finely tuned symmetrical facial expression that is so important for social acceptance. In an effort to improve outcomes a more conservative approach to facial rehabilitation has developed: 'Facial Neuromuscular Education' is a more conservative approach to treatment that emphasises symmetry in facial movements. This method has been tested against the conventional treatment package of more extreme facial exercises and electrical stimulation in a block randomised controlled trial of 59 patients. Patients in the experimental group were instructed to do actual facial movements on the affected side without allowing movements of the unaffected side to distort the symmetry. They were encouraged to concentrate on quality of the exercises and not the quantity, starting with only 5-10 repetitions of each exercise three times a day. For both groups the respective treatments were given in outpatient sessions for three weeks with continuation of training at home encouraged for three months. Measured using a facial grading scale in which facial symmetry is assessed the patients treated with the Facial Neuromuscular Education had significantly better (more symmetrical) facial movements at 3 months. The report does not indicate that assessors were blind to group allocation, nor does it give any idea of compliance to the treatments at home. It is also impossible to tell whether the electrical stimulation actually had a harmful effect, as has been suggested in animal studies. However the results suggest that the more controlled training of facial movements might yield better outcomes for patients with Bell's Palsy than the more gung ho practice of gross facial expressions and electrical stimulation. -*AJT*

Manikandan N.

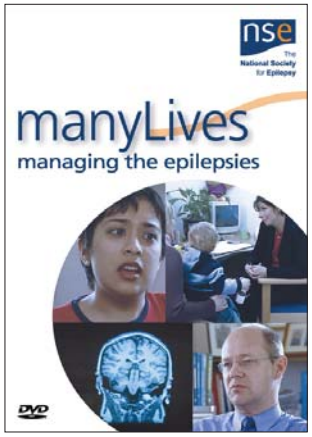
Effect of neuromuscular re-education on facial symmetry in patients with Bell's palsy: a randomised controlled trial.

CLINICAL REHABILITATION

2007:21:338-43.

News Review

Latest thinking on treating epilepsy at special price



A unique resource featuring some of the world's leading experts in epilepsy is now exclusively available from the National Society for Epilepsy (NSE) at a special one-off promotional price. The new three-disc education and information DVD package manyLives explores the latest thinking on the treatment of epilepsy.

Internationally recognised expert Professor John Duncan, featured, says manyLives is an ideal tool for neurologists, training neurologists and other health professionals who treat people with epilepsy. "This project is very exciting as it highlights the importance of those with epilepsy working with their professional advisors to devise the best treatment plan to try to control their epilepsy and to make the most of their life," Professor Duncan said.

The resource, featuring nine of the UK's leading experts in epilepsy, also contains information and downloadable practical tools for treating and managing the condition. It is supplemented by seizure footage to help with the recognition and classification of seizures.

NSE's epilepsy information manager Rona Gibb said: "It is a programme designed for professionals working within the multi disciplinary team that provides care for people with epilepsy. It reflects the move away from the old theory of adherence to the more recent idea of concordance."

People wishing to purchase manyLives at the special promotional price of £95 (normally £120) can visit the NSE online shop at www.epilepsynse.org.uk

Firewire entry-level digital cameras

The AxioCam IC digital microscope cameras

Boosting its range of AxioCam digital cameras, Carl Zeiss has launched a pair of entry-level cameras specially developed for routine applications in brightfield microscopy and stereomicroscopy. The 1.4 megapixel AxioCam ICc1 and the 3.3 megapixel AxioCam ICc3 combine outstanding performance and an affordable price, making them ideally suited for routine laboratory and industrial applications.

Both new cameras are inexpensive enough to replace conventional compact cameras with zoom lenses or complex video camera with framegrabber technology. However, resolutions of up to 2080x1540 pixels deliver a considerable improvement in image quality. The radical price/performance ratio means the AxioCam IC is ideally suited to the Zeiss Axio Star and Primo Star microscopes, the Stemi 2000C and SteREO Discovery stereomicroscopes, and routine microscopes and stereomicroscopes from other manufacturers.

The AxioCam IC cameras, measuring just 44x44x44mm, are equipped with C-mount adapters and are tightly integrated into Zeiss' AxioVision image processing software. A FireWire interface allows high speed transfer of up to 30 images per second with AxioCam ICc1 and 39 images per second with AxioCam ICc3. Since the cameras take power via the FireWire connection, a power cable or external PSU is not required.

Unlike video and compact cameras, the AxioCam IC operates without any moving parts and does not require memory cards or zoom adapters and correction procedures. The absence of moving parts offers totally vibration-free microscopy with distortionless images sent directly to the PC and the AxioVision application software.

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

Patients treated with Betaferon® after first MS attack experienced significant delay in disability progression

Patients treated with Betaferon® (interferon beta-1b) after their first clinical MS event or 'attack' showed a 40% lower risk of progressive neurological impairment as measured by the Expanded Disability Status Scale (EDSS), when compared to patients in whom treatment was delayed (p=0.022). The results, published recently in *The Lancet*, provide the first controlled evidence that delaying Betaferon® treatment has an effect on accumulation of disability. No other MS therapy has demonstrated this effect in this early patient population.

The BENEFIT study (BEtaferon in Newly Emerging multiple sclerosis For Initial Treatment), sponsored by Bayer Schering Pharma AG, compared Betaferon® treatment initiated after a first clinical event with delayed treatment. The study was conducted at 98 sites in 20 countries, including the UK, and included a total of 468 patients.

In the study, investigators measured MS progression of patient disability using a validated, well-established scale called EDSS. Disability progression was defined as an increase in a patient's EDSS score by at least one point that was confirmed after six months. A confirmed increase by one point in the EDSS scale can be an important and robust predictor of permanent and severe disability later in the disease.

"The data from BENEFIT not only supports the evidence that treatment with Betaferon® after the first clinical attack reduces the risk of subsequent MS attacks in the first year, but is also the first to demonstrate an impact on disability progression." said Professor David Bates, Professor of Clinical Neurology at the University of Newcastle upon Tyne, UK.

For more information
E. liz.tucker@bayerhealthcare.com

Magstim® are pioneers in nerve stimulation

A company can only be as forward-thinking as its people, which explains why Magstim has become the leading developer of magnetic stimulation technology. Constantly pushing the boundaries of research and development, the recently formed custom design team - Magstim Innovations - offers expert engineering and manufacturing capabilities to tackle bespoke projects.

Magstim's latest technological advance is the unique Air Film™ Coil based on research by Dr Reza Jalinous, Boston, USA. Designed to allow users to stimulate for extended periods of time, the self cooling coil offers researchers and clinicians a compact, easy-to-use manoeuvrable unit which enhance both magnetic stimulation research and therapeutic applications.

Magstim is also helping to provide researchers and students with a forum to discuss their findings by sponsoring "Neuromodulation and Brain Stimulation News" (NBS News). NBS News brings together ground breaking magnetic stimulation research and current news from around the world into one newsletter.

Your free copy of NBS News is included with this issue of ACNR. If it is missing,
E. andrew.thomas@magstim.com or
Tel. +44 (0)1994 240798.

New PMR website

A new website aimed at physicians practicing physical medicine and rehabilitation (PMR) in different parts of the world has recently been launch by Manoj Sivan, a rehabilitation medicine trainee currently working in Cambridge. The website www.pmrforum.com is an initiative towards developing a common platform for specialists from every region of the world to share knowledge and views in a vast and ever growing speciality. The aim is to keep everyone informed of the current developments and update knowledge on various aspects of the speciality.

To register visit the website www.pmrforum.com and register yourself on the Forum page for access to view and contribute to the international debate. To add information to the other pages, members are requested to email manojsivan@pmrforum.com and it will be updated on the relevant page.

Hybrid solution enhances nuclear medicine capabilities


Pictured with the Siemens Symbia T2 are staff from the Princess Alexandra Hospital in Harlow: (L to R) Anita Woollard, Senior Radiographer, Brian Peters, Senior Radiographer, Ray Winstone, actor, Paula Sandhu, Superintendent Radiographer, Dr C J Barber, Consultant Radiologist, Liz Mazura, Radiology Manager, Gordon Flack, Finance Director and Chris Nottage, Consultant Physicist.

Siemens Medical Solutions has installed the Symbia T2 integrated gamma camera and dual slice CT scanner at Princess Alexandra Hospital in Harlow. TV and screen actor and local resident Ray Winstone lent his support at the official handover.

Princess Alexandra Hospital was keen to replace its previous system in order to provide more accurate diagnosis for its nuclear medicine service. The new technology will enable radiologists and clinicians to perform structural scans with CT superimposed on the Nuclear Medicine study, which guarantees greater accuracy in locating the lesions detected.

Symbia T2, a True Point SPECT·CT system, combines a dual-detector variable angle gamma camera with a dual slice CT scanner for routine oncology, neurology and cardiology applications. The device performs abdominal CT in less than 13 seconds and includes a dual slice 0.8 second rotation, with effective imaging of the new targeted tracers and agents.

For more information
Tel. +44 (0)1344 396317 or see www.siemens.com

Fast and efficient laser scanning microscopy

The LSM 5 DUO laser scanning microscope system based on the Zeiss AxioObserver platform.

Carl Zeiss has upgraded and enhanced its flagship laser scanning microscope with the release of the LSM 5 DUO R4.2. The new system boasts improved laser modules, increased resolution of 2.4 megapixels in the fast line scan mode, and an integrated autofocus function to make using many new fluorescent dyes faster and more efficient.

Consisting of two award-winning confocal microscope systems - the LSM 510 META and the LSM 5 LIVE, the LSM 5 DUO is ideal for combining fast scanning with optical sample manipulation for bleaching and for applications such as Photo-Activation, Photo-conversion, FRAP and FRET. Researchers wishing to use multiple fluorescent dyes will also benefit from the integration of several double bandpass filters into the DUO. Fast excitation wavelength changes allow imaging of two dyes through only one detection channel or up to four dyes through two detection channels.

The LSM 510 META and LSM 5 LIVE are also available as individual systems and now feature improved hardware and software.

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

World's first high definition PET•CT unveiled

The Biograph 64 PET•CT scanner used in conjunction with syngo TrueD software.

Siemens Medical Solutions has introduced high definition positron emission tomography with the recent unveiling of HD•PET, the world's first and only high definition PET technology to offer consistently sharper and clearly defined images across the entire field of view.

Siemens has added high definition to the Biograph™ TruePoint™ family of hybrid PET•CT systems. The clarity of HD•PET will provide greater specificity and accuracy and will enable physicians to more confidently delineate small lesions – including those in lymph nodes, abdomen, head and neck and brain – to provide earlier, more targeted treatment.

The clarity achieved by HD•PET is the result of a unique and proprietary technology that optimises the elements of image uniformity, resolution and contrast - that together change the whole picture.

The uniform resolution provided by HD•PET throughout the field-of-view is a significant step in improving PET image quality. This could potentially improve staging of disease and hence clinical outcome.

By utilising a proprietary reconstruction technique, HD•PET can provide distortion-free images throughout the entire field of view. This improved 2 mm resolution enables physicians to clearly visualise the smallest of lesions from the centre to the edges - a benefit unique to Siemens' HD•PET.

Adding high definition to PET systems also dramatically enhances contrast. The improvement in signal to noise, which effectively doubles, reveals sharper images that allow the clinician to better differentiate between healthy and suspicious tissue.

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ABBREVIATED PRESCRIBING INFORMATION
ARICEPT® EVESS® (donepezil hydrochloride orodispersible tablet)
Please refer to the SmPC before prescribing ARICEPT EVESS 5 mg or ARICEPT EVESS 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. Orodispersible tablet which should be placed on the tongue and allowed to disintegrate before swallowing with or without water. Treatment should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Pregnancy:** Aricept should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, ability to drive/operate machinery should be routinely evaluated. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT EVESS 5 mg; white, embossed, orodispersible tablets, packs of 28 £63.54. ARICEPT EVESS 10 mg; yellow, embossed, orodispersible tablets, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT EVESS 5 mg; PL 10555/0019 ARICEPT EVESS 10 mg; PL 10555/0020. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** December 2006

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. Aricept SmPC **2.** Aricept Evess SmPC **3.** Rivastigmine SmPC **4.** Galantamine SmPC **5.** Galantamine XL SmPC **6.** Memantine SmPC **7.** Data on File Studies 015, 016 and 017 (Eisai Ltd, Pfizer Ltd)

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